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FILE 'CAPLUS' ENTERED AT 21:01:57 ON 11 JUL 2002
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FILE 'USPATFULL' ENTERED AT 21:01:57 ON 11 JUL 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l2 and (glucocorticoid? or nsaid# or bronchodilator? or antibiotic?)
L9          64 L2 AND (GLUCOCORTICOID? OR NSAID# OR BRONCHODILATOR? OR ANTIBIOT
               IC?)

=> s l2(p)(glucocorticoid? or nsaid# or bronchodilator? or antibiotic?)
L10         24 L2(P)(GLUCOCORTICOID? OR NSAID# OR BRONCHODILATOR? OR ANTIBIOTIC
               ?)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11          24 DUP REM L10 (0 DUPLICATES REMOVED)

=> d scan l11
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FILE 'STNGUIDE' ENTERED AT 20:45:33 ON 11 JUL 2002

FILE 'STNGUIDE' ENTERED AT 20:56:41 ON 11 JUL 2002
L8 0 S L2 AND (GLUCOCORTICOID? OR NSAID# OR BRONCHODILATOR? OR ANTIB

FILE 'CAPLUS, USPATFULL' ENTERED AT 21:01:57 ON 11 JUL 2002
L9 64 S L2 AND (GLUCOCORTICOID? OR NSAID# OR BRONCHODILATOR? OR ANTIB
L10 24 S L2(P)(GLUCOCORTICOID? OR NSAID# OR BRONCHODILATOR? OR ANTIBIO
L11 24 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 abs ibib kwic 1-24

L11 ANSWER 1 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB A method is provided for treating inflammatory respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD). The method involves administration, preferably oral or pulmonary administration, of an active agent selected from the group consisting of resveratrol, pharmacol. acceptable salts, esters, amides, prodrugs and analogs thereof, and combinations of any of the foregoing. Pharmaceutical formulations for use in conjunction with the aforementioned method are provided as well.
ACCESSION NUMBER: 2002:314756 CAPLUS
DOCUMENT NUMBER: 136:319401
TITLE: Administration of resveratrol to treat inflammatory respiratory disorders
INVENTOR(S): Donnelly, Louise Elizabeth; Barnes, Peter John
PATENT ASSIGNEE(S): Imperial College Innovations Limited, UK
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002032410 | A2 | 20020425 | WO 2001-GB4672 | 20011019 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-694108 A 20001019
IT Macrolides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**antibiotics**; **resveratrol** treatment of inflammatory respiratory disorders)
IT **Antibiotics**
(macrolide; **resveratrol** treatment of inflammatory respiratory disorders)
IT Antiasthmatics
Asthma
**Bronchodilators**
Concrete

Dust
Emphysema
Flours and Meals
Human
Tobacco smoke
Wood
(**resveratrol** treatment of inflammatory respiratory disorders)

IT **Glucocorticoids**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**resveratrol** treatment of inflammatory respiratory disorders)

L11 ANSWER 2 OF 24 USPATFULL

AB It has been discovered that the stimulation of .beta.-adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes. Hence, the in vitro or in vivo exposure of neuronal cells to certain compositions comprising .beta.-adrenergic receptor ligands or agonists, including, e.g., norepinephrine, isoproterenol and the like, increases APP mRNA transcription and consequent APP overproduction. These increases are blocked by .beta.-adrenergic receptor antagonists, such as propranolol. The in vitro or in vivo treatment of these cells with 8Br-cAMP, prostaglandin E.sub.2 (PG E.sub.2), forskolin, and nicotine ditartrate also increased APP synthesis, including an increase in mRNA and holoprotein levels, as well as an increase in the expression of glial fibrillary acidic protein (GFAP). Compositions and methods are disclosed of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of .beta.-adrenergic receptors. It has further been found that the increase in APP synthesis caused by 8Br-cAMP, PG E.sub.2, or forskolin is inhibited by immunosuppressants, immunophilin ligands, or anti-inflammatory agents, such as cyclosporin A, and FK-506 (tacrolimus), as well as ion-channel modulators, including ion chelating agents such as EGTA, or calcium/calmodulin kinase inhibitors, such as KN93. The present invention has broad implications in the alleviation, treatment, or prevention of neurological disorders and neurodegenerative diseases, including Alzheimer's Disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:99506 USPATFULL
TITLE: Compositions and methods for treatment of neurological disorders and neurodegenerative diseases
INVENTOR(S): Lee, Robert K.K., Boston, MA, UNITED STATES
Wurtman, Richard J., Boston, MA, UNITED STATES
PATENT ASSIGNEE(S): Massachusetts Institute of Technology (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002052407 | A1 | 20020502 |
| APPLICATION INFO.: | US 2001-775809 | A1 | 20010205 (9) |

RELATED APPLN. INFO.: Continuation of Ser. No. US 1999-435470, filed on 8 Nov 1999, PATENTED Continuation-in-part of Ser. No. US 1997-924505, filed on 5 Sep 1997, PATENTED

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1996-25507P | 19960905 (60) |
| | US 1997-33765P | 19970115 (60) |

09/694,108

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: KATTEN MUCHIN ZAVIS, 525 WEST MONROE STREET SUITE 600, CHICAGO, IL, 60661-3693
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 18 Drawing Page(s)
LINE COUNT: 1807
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM [0018] Epidemiologic and clinical data suggest that the use non-steroidal anti-inflammatory drugs (**NSAIDs**) delays the onset of AD and reduces the progression of pathologic symptoms in Alzheimer's disease. McGeer and McGeer, Brain Res. Rev. 21, 195 (1995). Aspirin, like most **NSAIDs**, prevent inflammation and pain by inhibiting both COX-1 and COX-2 enzymes. **Resveratrol**, a phenolic antioxidant and COX inhibitor found in grapes, inhibits prostaglandin production, and has anti-cancer and anti-inflammatory properties. Jang et. . .

SUMM [0033] It has still further been discovered that non-steroidal antiinflammatory agents (**NSAIDS**), such as specific inhibitors of cyclo-oxygenase type 2 activity including, but not limited to, DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl-2(5H)-furanone), DFP (5,5-dimethyl-3-isopropyloxy-4-(4'-methylsulfonylphenyl)-2(5H)-furanone), and **resveratrol**, can also prevent APP overexpression and the overproduction of amyloidogenic peptides.

DETD [0073] Aspirin, like most **NSAIDs**, inhibits both COX-1 and COX-2 enzymes. Cultured astrocytes or neurons are treated with aspirin or **resveratrol** for 1 h (at nano- or micromolar range), resulting in an increase in the secretion of soluble APPs (as measured by Western blot analysis). The increase in APPs secretion caused by aspirin or **resveratrol** is accompanied by a decreased levels of cellular and amyloidogenic APP holoprotein (FIG. 16). Thus, **NSAIDs** stimulate non-amyloidogenic APP processing in vitro.

DETD [0173] Cultured astrocytes or neurons are treated with aspirin or **resveratrol** for 1 h (at nano- or micromolar range), and secretion of soluble APPs is measured by Western blot analysis. The increase in APPs secretion caused by aspirin or **resveratrol** is accompanied by decreased levels of cellular and amyloidogenic APP holoprotein (FIG. 16). Thus, **NSAIDs** appear to stimulate non-amyloidogenic APP processing in vitro.

L11 ANSWER 3 OF 24 USPATFULL

AB The present invention concerns compositions suitable for topical application, comprising glucosylated hydroxystilbenes. It also concerns a method for slowly releasing hydroxystilbenes into the stratum corneum, by applying a composition comprising glucosylated hydroxystilbenes as a precursor. Finally, it concerns the use of glucosylated hydroxystilbenes to combat signs of cutaneous and hair follicle ageing, to improve the radiance of the skin, to smooth the skin of the face, to treat or prevent wrinkles and fine lines in the skin or to stimulate the epidermal renewal process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2002:98904 USPATFULL
TITLE: Glucosylated hydroxystilbene compounds for treating skin conditions
INVENTOR(S): Pruche, Francis, Senlis, FRANCE
Bernard, Dominique, Paris, FRANCE

Mehul, Bruno, Villejuif, FRANCE

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002051799 | A1 | 20020502 |
| APPLICATION INFO.: | US 2001-915353 | A1 | 20010727 (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | FR 2000-10008 | 20000728 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Norman H. Stepno, Esquire, BURNS, DOANE, SWECKER & MATHIS, L.L.P., P.O. Box 1404, Alexandria, VA, 22313-1404
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
LINE COUNT: 445
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM [0002] Stilbenes and glucosylated stilbenes are produced in plants, essentially in spermatophytes, and constitute a member of the class of **antibiotic** molecules known as phytoalexins. A well documented member of this class is **resveratrol**, or 3,4',5-trihydroxystilbene.

L11 ANSWER 4 OF 24 USPATFULL
AB A method is provided for preventing or treating skin conditions, disorders or diseases, such as may be associated with or caused by inflammation, sun damage or natural aging. The method involves administration, preferably topical administration, of an active agent selected from the group consisting of resveratrol, pharmacologically acceptable salts, esters, amides, prodrugs and analogs thereof, and combinations of any of the foregoing. Pharmaceutical formulations for use in conjunction with the aforementioned method are provided as well.

ACCESSION NUMBER: 2002:160783 USPATFULL
TITLE: Pharmaceutical formulations of resveratrol and methods of use thereof
INVENTOR(S): Pezzuto, John M., River Forest, IL, United States
Moon, Richard C., Plant City, FL, United States
Jang, Mei-Shiang, Chicago, IL, United States
Ouali, Aomar, Montreal, CANADA
Lin, Shengzhao, Montreal, CANADA
Barillas, Karla Slowing, Madrid, SPAIN
PATENT ASSIGNEE(S): Pharmascience, Montreal, CANADA (non-U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6414037 | B1 | 20020702 |
| APPLICATION INFO.: | US 1999-430337 | | 19991029 (9) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1998-5114, filed on 9 Jan 1998, now patented, Pat. No. US 6008260
DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Fay, Zohreh
ASSISTANT EXAMINER: Kwon, Brian-Yong
LEGAL REPRESENTATIVE: Reed, Dianne E., Hartrum, J. Elin, Reed & Associates
NUMBER OF CLAIMS: 37

09/694,108

EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 1142

SUMM In addition, **resveratrol** has found to be useful as a cancer chemopreventive agent. Known cancer chemopreventive agents include nonsteroidal antiinflammatory drugs (**NSAIDs**) such as indomethacin, aspirin, piroxicam, and sulindac, all of which inhibit cyclooxygenase, abbreviated hereafter as COX. A COX inhibitory activity. . . derived from Cassia quinquatngilata Rich. (Leguminosae) was identified as a potent COX inhibitor, and on the basis of bioassay-guided fractionation, trans-**resveratrol** was identified as the active compound. See Mannila et al. (19983) Phytochemistry 33:813, and Jayatilake et al. (1993), J. Nat.. . .

DETD **Resveratrol** was found to inhibit cellular events associated with tumor initiation, promotion, and progression. As discussed hereafter, the activity of **resveratrol** was demonstrated on the basis of ability of **resveratrol** to inhibit the cyclooxygenase activity of COX-1 (i.e., median effective dose ED.sub.50 of 15 .mu.M). This activity correlates with antitumor promotion. Although the inhibitory activity of **resveratrol** was less than that of some **NSAIDs**, such as indomethacin (ED.sub.50=2.3 .mu.M), the **resveratrol** activity was much greater than the activity of compounds such as aspirin (ED.sub.50=880 .mu.M). Also, unlike indomethacin and most other **NSAIDs**, **resveratrol** inhibited the hydroperoxidase activity of COX-1 (ED.sub.50=3.7 .mu.M).

L11 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB In addn. to antagonizing inflammation by inhibiting the activity of cyclooxygenases (COX), nonsteroidal anti-inflammatory drugs (NSAID) block T-cell activation. The immunosuppressant activity of NSAID correlates with their ability to block transcription factors required for the expression of inducible response genes triggered by T-cell antigen receptor (TCR) engagement. Whereas the inhibition of nuclear factor-.kappa.B by aspirin and sodium salicylate can be partly accounted for by their binding to I.kappa.B kinase-.beta., the broad range of transcriptional targets of NSAID suggests that the products of COX activity might affect 1 or more among the early steps in the TCR-signaling cascade. Here the authors show that the inhibition of NF-AT activation by NSAID correlates with a selective inhibition of p38 MAP kinase induction. The suppression of TCR-dependent p38 activation by NSAID can be fully overcome by prostaglandin E2, underlining the requirement for COX activity in p38 activation. Furthermore, the inhibition of COX-1 results in defective induction of the COX-2 gene, which behaves as an early TCR responsive gene. The data identify COX-1 and COX-2 as integral and sequential components of TCR signaling to p38 and contribute to elucidate the mol. basis of immunosuppression by NSAID.

ACCESSION NUMBER: 2002:79804 CAPLUS
DOCUMENT NUMBER: 136:303760
TITLE: Nonsteroidal anti-inflammatory drugs suppress T-cell activation by inhibiting p38 MAPK induction
AUTHOR(S): Paccani, Silvia Rossi; Boncristiano, Marianna; Ulivieri, Cristina; D'Elios, Mario Milco; Del Prete, Gianfranco; Baldari, Cosima T.
CORPORATE SOURCE: Department of Evolutionary Biology, University of Siena, Siena, 53100, Italy
SOURCE: Journal of Biological Chemistry (2002), 277(2), 1509-1513
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 50-78-2, Acetylsalicylic acid **501-36-0, Resveratrol**
15687-27-1, Ibuprofen 123653-11-2, NS-398 152121-47-6, SB203580
167869-21-8, PD098059
RL: DMA (Drug mechanism of action); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**NSAIDs** suppress T-cell activation by inhibiting p38 MAPK induction)

L11 ANSWER 6 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB Exposure of HepG2 cells to nonsteroidal anti-inflammatory drugs (i.e., indomethacin and ibuprofen; **NSAIDs**) as well as **resveratrol**, caused increased expression of the mRNAs coding for the catalytic (Gclc) and modifier (Gclm) subunits of the glutathione synthetic enzyme, .gamma.-glutamylcysteine synthetase. In addn., indomethacin exposure increased intracellular glutathione content as well as inhibited glutathione depletion and cytotoxicity caused by di-Et maleate. Indomethacin-induced increases in the expression of .gamma.-glutamylcysteine synthetase mRNA were preceded by increases in steady state levels of intracellular pro-oxidants and glutathione disulfide accumulation. Simultaneous incubation with the thiol antioxidant N-acetylcysteine (NAC) inhibited indomethacin-mediated increases in GCLC mRNA, suggesting that increases in GCLC message were triggered by changes in intracellular oxidn./redn. (redox) reactions. Indirect immunofluorescence using intact cells demonstrated that indomethacin induced the nuclear translocation of Nrf2, a transcription factor believed to regulate GCLC expression. Immunopptn. studies showed that indomethacin treatment also inhibited Nrf2 tethering to KIAA0132 (the human homolog of Keap1 accession D50922), which is believed to be a neg. regulator of Nrf2. Consistent with this idea, over-expression of Nrf2 increased GCLC reporter gene expression and over-expression of KIAA0132 inhibited GCLC reporter gene activity as well as inhibited indomethacin-induced increases in the expression of GCLC. Finally, simultaneous treatment with NAC inhibited both indomethacin-induced release of Nrf2 from KIAA0132 and indomethacin-induced nuclear translocation of Nrf2. These results demonstrate that **NSAIDs** and **resveratrol** cause increases in the expression of .gamma.-glutamylcysteine synthetase mRNA and identify these agents as being capable of stimulating glutathione metab. These results also support the hypothesis that indomethacin-induced transcriptional activation of GCLC involves the redox-dependent release of KIAA0132 from Nrf2 followed by the nuclear translocation of Nrf2.

ACCESSION NUMBER: 2002:211640 CAPLUS
TITLE: Redox-sensitive interaction between KIAA0132 and Nrf2 mediates indomethacin-induced expression of .gamma.-glutamylcysteine synthetase
AUTHOR(S): Sekhar, Konjeti R.; Spitz, Douglas R.; Harris, Stephanie; Nguyen, Trung T.; Meredith, Michael J.; Holt, Jeffrey T.; Guis, David; Marnett, Lawrence J.; Summar, Marshall L.; Freeman, Michael L.
CORPORATE SOURCE: Dept of Radiation Oncology, Vanderbilt University School of Medicine, Nashville, TN, USA
SOURCE: Free Radical Biology & Medicine (2002), 32(7), 650-662

CODEN: FRBMEH; ISSN: 0891-5849
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Exposure of HepG2 cells to nonsteroidal anti-inflammatory drugs (i.e., indomethacin and ibuprofen; **NSAIDs**) as well as **resveratrol**, caused increased expression of the mRNAs coding for the catalytic (Gclc) and modifier (Gclm) subunits of the glutathione synthetic enzyme, .gamma.-glutamylcysteine synthetase. In addn., indomethacin exposure increased intracellular glutathione content as well as inhibited glutathione depletion and cytotoxicity caused by di-Et maleate. Indomethacin-induced increases in the expression of .gamma.-glutamylcysteine synthetase mRNA were preceded by increases in steady state levels of intracellular pro-oxidants and glutathione disulfide accumulation. Simultaneous incubation with the thiol antioxidant N-acetylcysteine (NAC) inhibited indomethacin-mediated increases in GCLC mRNA, suggesting that increases in GCLC message were triggered by changes in intracellular oxidn./redn. (redox) reactions. Indirect immunofluorescence using intact cells demonstrated that indomethacin induced the nuclear translocation of Nrf2, a transcription factor believed to regulate GCLC expression. Immunopptn. studies showed that indomethacin treatment also inhibited Nrf2 tethering to KIAA0132 (the human homolog of Keap1 accession D50922), which is believed to be a neg. regulator of Nrf2. Consistent with this idea, over-expression of Nrf2 increased GCLC reporter gene expression and over-expression of KIAA0132 inhibited GCLC reporter gene activity as well as inhibited indomethacin-induced increases in the expression of GCLC. Finally, simultaneous treatment with NAC inhibited both indomethacin-induced release of Nrf2 from KIAA0132 and indomethacin-induced nuclear translocation of Nrf2. These results demonstrate that **NSAIDs** and **resveratrol** cause increases in the expression of .gamma.-glutamylcysteine synthetase mRNA and identify these agents as being capable of stimulating glutathione metab. These results also support the hypothesis that indomethacin-induced transcriptional activation of GCLC involves the redox-dependent release of KIAA0132 from Nrf2 followed by the nuclear translocation of Nrf2.

L11 ANSWER 7 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB Dietary phenolic substances including **resveratrol**, a stillbene compd., are found in several fruits and vegetables, and these compds. have been reported to have anti-oxidant, anti-inflammatory and antitumorigenic activities. However, the mol. mechanisms underlying the antitumorigenic or chemopreventive activities of these compds. remain largely unknown. The expression of NAG-1 [non-steroidal anti-inflammatory (**NSAID**) drug-activated gene-1], a member of the transforming growth factor-beta (TGF-.beta.) superfamily, has been shown to be assocd. with pro-apoptotic and antitumorigenic activities. Here, we have demonstrated that **resveratrol** induces NAG-1 expression and apoptosis in a concn.-dependent manner. **Resveratrol** increases the expression of p53, tumor suppressor protein, prior to NAG-1 induction, indicating that NAG-1 expression by **resveratrol** is mediated by p53 expression. We also show that the p53 binding sites within the promoter region of NAG-1 play a pivotal role to control NAG-1 expression by **resveratrol**. Derivs. of **resveratrol** were examd. for NAG-1 induction, and the data suggest that **resveratrol**-induced NAG-1 and p53 induction is not dependent on its anti-oxidant activity.

The data may provide linkage between p53, NAG-1 and **resveratrol**, and in part, a new clue to the mol. mechanism of the antitumorigenic activity of natural polyphenolic compds.

ACCESSION NUMBER: 2002:266464 CAPLUS
TITLE: Resveratrol enhances the expression of non-steroidal anti-inflammatory drug-activated gene (NAG-1) by increasing the expression of p53
AUTHOR(S): Baek, Seung Joon; Wilson, Leigh C.; Eling, Thomas E.
CORPORATE SOURCE: Laboratory of Molecular Carcinogenesis, National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, NC, 27709, USA
SOURCE: Carcinogenesis (2002), 23(3), 425-434
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Dietary phenolic substances including **resveratrol**, a stillbene compd., are found in several fruits and vegetables, and these compds. have been reported to have anti-oxidant, anti-inflammatory and antitumorigenic activities. However, the mol. mechanisms underlying the antitumorigenic or chemopreventive activities of these compds. remain largely unknown. The expression of NAG-1 [non-steroidal anti-inflammatory (**NSAID**) drug-activated gene-1], a member of the transforming growth factor-beta (TGF-.beta.) superfamily, has been shown to be assocd. with pro-apoptotic and antitumorigenic activities. Here, we have demonstrated that **resveratrol** induces NAG-1 expression and apoptosis in a concn.-dependent manner. **Resveratrol** increases the expression of p53, tumor suppressor protein, prior to NAG-1 induction, indicating that NAG-1 expression by **resveratrol** is mediated by p53 expression. We also show that the p53 binding sites within the promoter region of NAG-1 play a pivotal role to control NAG-1 expression by **resveratrol**. Derivs. of **resveratrol** were examd. for NAG-1 induction, and the data suggest that **resveratrol**-induced NAG-1 and p53 induction is not dependent on its anti-oxidant activity. The data may provide linkage between p53, NAG-1 and **resveratrol**, and in part, a new clue to the mol. mechanism of the antitumorigenic activity of natural polyphenolic compds.

L11 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB We have cloned a novel ABC transporter gene PMR5 from the phytopathogenic fungus Penicillium digitatum by RT-PCR using degenerate primers. The deduced amino acid sequence of PMR5 showed 37% identity to PMR1 from the same fungus, 71% identity to AtrB from Aspergillus nidulans, and 65% identity to BcatrB from Botrytis cinerea. Disruption mutants for PMR5 were generated in two independent P. digitatum strains and their phenotypes were characterized. These mutants displayed increased sensitivity to thiabendazole (a benzimidazole), benomyl (a benzimidazole), dithianon (a quinone), **resveratrol** (the phytoalexin of grape), and camptothecin (an alkaloid). .DELTA.pmr1 disruption mutants were previously reported to show resistance to demethylation inhibitors (DMIs). These mutants were found also to display increased sensitivity to phloretin (the phytoanticipin of apples), camptothecin and oligomycin (an **antibiotic**). Transcription of PMR1 and PMR5 was strongly induced in response to several toxicants, including DMIs that specifically induced PMR1. In contrast, dithianon and **resveratrol** specifically

induced PMR5 transcription. These findings indicate that expression of the two ABC transporter genes is regulated differently, and that they have complementary roles in multidrug resistance, with each having different substrate-specificities.

ACCESSION NUMBER: 2002:483468 CAPLUS
TITLE: A novel ABC transporter gene, PMR5, is involved in multidrug resistance in the phytopathogenic fungus Penicillium digitatum
AUTHOR(S): Nakaune, R.; Hamamoto, H.; Imada, J.; Akutsu, K.; Hibi, T.
CORPORATE SOURCE: Laboratory of Plant Pathology, Department of Grape and Persimmon Research, National Institute of Fruit Tree Science, Hiroshima, 729-2494, Japan
SOURCE: Molecular Genetics and Genomics (2002), 267(2), 179-185
CODEN: MGGOAA; ISSN: 1617-4615
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB We have cloned a novel ABC transporter gene PMR5 from the phytopathogenic fungus Penicillium digitatum by RT-PCR using degenerate primers. The deduced amino acid sequence of PMR5 showed 37% identity to PMR1 from the same fungus, 71% identity to AtrB from Aspergillus nidulans, and 65% identity to BcatrB from Botrytis cinerea. Disruption mutants for PMR5 were generated in two independent P. digitatum strains and their phenotypes were characterized. These mutants displayed increased sensitivity to thiabendazole (a benzimidazole), benomyl (a benzimidazole), dithianon (a quinone), **resveratrol** (the phytoalexin of grape), and camptothecin (an alkaloid). .DELTA.pmr1 disruption mutants were previously reported to show resistance to demethylation inhibitors (DMIs). These mutants were found also to display increased sensitivity to phloretin (the phytoanticipin of apples), camptothecin and oligomycin (an **antibiotic**). Transcription of PMR1 and PMR5 was strongly induced in response to several toxicants, including DMIs that specifically induced PMR1. In contrast, dithianon and **resveratrol** specifically induced PMR5 transcription. These findings indicate that expression of the two ABC transporter genes is regulated differently, and that they have complementary roles in multidrug resistance, with each having different substrate-specificities.

L11 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB A method is provided for preventing, delaying, or reversing the progression of Alzheimer's disease by administering an A.beta.42-lowering agent to a mammal under conditions in which levels of A.beta.42 are selectively reduced, levels of A.beta.38 are increased, and levels of A.beta.40 are unchanged. The invention provides methods and materials for developing and identifying A.beta.42-lowering agents. In addn., the invention provides methods for identifying agents that increase the risk of developing, or hasten progression of, Alzheimer's disease. The invention also provides compns. of A.beta.42-lowering agents and antioxidants, A.beta.42 lowering agents and non-selective secretase inhibitors, and A.beta.42 lowering agents and acetylcholinesterase inhibitors. The invention further provides kits contg. A.beta.42-lowering agents, antioxidants, non-selective secretase inhibitors, and/or acetylcholinesterase inhibitors as well as instructions related to dose regimens for A.beta.42-lowering agents, antioxidants, non-selective

secretase inhibitors, and acetylcholinesterase inhibitors. The agents of the invention include nonsteroidal antiinflammatory drugs (NSAIDs) and NSAID derivs.

ACCESSION NUMBER: 2001:780679 CAPLUS
DOCUMENT NUMBER: 135:327362
TITLE: Nonsteroidal antiinflammatory drug (NSAID) and NSAID derivative amyloid A.beta.42 polypeptide-lowering agents for the treatment of Alzheimer's disease, and screening methods
INVENTOR(S): Koo, Edward Hao Mang; Golde, Todd Eliot; Galasko, Douglas Roger
PATENT ASSIGNEE(S): Mayo Foundation for Medical Education and Research, USA
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001078721 | A1 | 20011025 | WO 2001-US11956 | 20010412 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-196617P P 20000413
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 50-78-2, Aspirin 80-08-0, Dapsone 489-84-9, Guaiazulene
**501-36-0, Resveratrol** 642-72-8, Benzydamine
4394-00-7, Niflumic acid 13710-19-5, Tolfenamic acid 15307-86-5, Diclofenac 22071-15-4, Ketoprofen 22204-53-1, Naproxen 22494-42-4, Diflunisal 27470-51-5, Suxibuzone 31842-01-0, Indoprofen 34552-84-6, Isoxicam 36322-90-4, Piroxicam 36330-85-5, Fenbufen 40828-46-4, Suprofen 41340-25-4, Etodolac 42924-53-8, Nabumetone 51803-78-2, Nimesulide 53164-05-9, Acemetacin 59804-37-4, Tenoxicam 59973-80-7, Sulindac sulfone 71125-38-7, Meloxicam 74103-06-3, Ketorolac 123653-11-2, NS-398 162011-90-7, Rofecoxib 169590-42-5, Celecoxib 188817-13-2, SC560 209125-28-0
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**NSAID** and **NSAID** deriv. amyloid A.beta.42 polypeptide-lowering agents for treatment of Alzheimer's disease, and screening methods)

L11 ANSWER 10 OF 24 USPATFULL
AB The use of resveratrol (3,4',5-trihydroxy-trans-stilbene) and derivatives thereof, for the preparation of medicaments for the treatment of exfoliative eczema, acne and psoriasis, topical pharmaceutical formulations containing resveratrol or derivatives thereof in combination with other active principles. Treatment consists

in topical administrations of resveratrol at concentrations of 0.01 to 20%, in the form of lotions, creams or ointments, optionally in combination with other active principles such as melatonin, vitamins D, E and A and derivatives thereof, hormones, vegetable and/or animal extracts. Contrary to current therapies, the use of resveratrol has neither systemic nor topical effects during and after therapy.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2001:237951 USPATFULL | | |
| TITLE: | Use of resveratrol for the treatment of exfoliative eczema, acne and psoriasis | | |
| INVENTOR(S): | Pelliccia, Maria Teresa, Avellino, Italy<br>Giannella, Attilio, Codogno, Italy<br>Giannella, Jenny, Codogno, Italy | | |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2001056071 | A1 | 20011227 | |
| APPLICATION INFO.: | US 2001-813948 | A1 | 20010322 | (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | IT 2000-MI2000000630200000324 | |

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|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |
| LEGAL REPRESENTATIVE: | YOUNG & THOMPSON, 745 SOUTH 23RD STREET 2ND FLOOR, ARLINGTON, VA, 22202 |
| NUMBER OF CLAIMS: | 8 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 329 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD [0025] A randomized, double blind study was carried out in order to evaluate the effectiveness of topical administration of **resveratrol** in the treatment of acne vulgaris. Patients (n=30) of 15 to 19 years were all suffering from II or III. . . a number of comedos (28 to 120) on face and forehead. Only subjects who had received no systemic treatment with **antibiotics** for at least 4 weeks and had used no topical medicaments for 2 weeks before treatment were selected. During treatment with **resveratrol**, no further topical treatment was allowed. The effectiveness of the therapy was evaluated by comparing the conditions of the lesions. . .

L11 ANSWER 11 OF 24 USPATFULL

AB It has been discovered that the stimulation of .beta.adrenergic receptors, which activate cAMP formation, give rise to increased APP and GFAP synthesis in astrocytes. Hence, the in vitro or in vivo exposure of neuronal cells to certain compositions comprising .beta.-adrenergic receptor ligands or agonists, including, e.g., norepinephrine, isoproterenol and the like, increases APP mRNA transcription and consequent APP overproduction. These increases are blocked by .beta.-adrenergic receptor antagonists, such as propranolol. The in vitro or in vivo treatment of these cells with 8Br-cAMP, prostaglandin E.sub.2 (PG E.sub.2), forskolin, and nicotine ditartrate also increased APP synthesis, including an increase in mRNA and holoprotein levels, as well as an increase in the expression of glial fibrillary acidic protein (GFAP). Compositions and methods are disclosed of regulating APP overexpression and mediating reactive astrogliosis through cAMP signaling or the activation of .beta.-adrenergic receptors. It has

further been found that the increase in APP synthesis caused by 8Br-cAMP, PG E.sub.2, or forskolin is inhibited by immunosuppressants, immunophilin ligands, or anti-inflammatory agents, such as cyclosporin A, and FK-506 (tacrolimus), as well as ion-channel modulators, including ion chelating agents such as EGTA, or calcium/calmodulin kinase inhibitors, such as KN93. The present invention has broad implications in the alleviation, treatment, or prevention of neurological disorders and neurodegenerative diseases, including Alzheimer's Disease.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 2001:18494 USPATFULL |
| TITLE: | Compositions and methods for treatment of neurological disorders and neurodegenerative diseases |
| INVENTOR(S): | Lee, Robert K. K., 3 Union Park, Apt#1, Boston, MA, United States 02118<br>Wurtman, Richard J., Heritage on the Garden, 300 Boylston St., #1205, Boston, MA, United States 02116 |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6184248 | B1 | 20010206 |
| APPLICATION INFO.: | US 1999-435470 | | 19991108 (9) |
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 1997-924505, filed on 5 Sep 1997, now patented, Pat. No. US 6043224 | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1996-25507P | 19960905 (60) |
| | US 1997-33765P | 19970115 (60) |

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| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Reamer, James H. |
| LEGAL REPRESENTATIVE: | Villacorta, Gilberto M.Pepper Hamilton LLP |
| NUMBER OF CLAIMS: | 19 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 36 Drawing Figure(s); 30 Drawing Page(s) |
| LINE COUNT: | 1830 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Epidemiologic and clinical data suggest that the use non-steroidal anti-inflammatory drugs (**NSAIDs**) delays the onset of AD and reduces the progression of pathologic symptoms in Alzheimer's disease. McGeer and McGeer, Brain Res. Rev. 21, 195 (1995). Aspirin, like most **NSAIDs**, prevent inflammation and pain by inhibiting both COX-1 and COX-2 enzymes. **Resveratrol**, a phenolic antioxidant and COX inhibitor found in grapes, inhibits prostaglandin production, and has anti-cancer and anti-inflammatory properties. Jang et. . .

SUMM It has still further been discovered that non-steroidal antiinflammatory agents (**NSAIDS**), such as specific inhibitors of cyclo-oxygenase type 2 activity including, but not limited to, DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulfonyl)phenyl-2(5H)-furanone), DFP (5,5-dimethyl-3-isopropyloxy-4-(4'-methylsulfonylphenyl)-2(5H)-furanone), and **resveratrol**, can also prevent APP overexpression and the overproduction of amyloidogenic peptides.

DETD Aspirin, like most **NSAIDs**, inhibits both COX-1 and COX-2 enzymes. Cultured astrocytes or neurons are treated with aspirin or **resveratrol** for 1 h (at nano- or micromolar range), resulting in an increase in the secretion of soluble APPs (as measured by Western blot analysis). The increase in APPs secretion caused by aspirin or

**resveratrol** is accompanied by a decreased levels of cellular and amyloidogenic APP holoprotein (FIG. 16). Thus, **NSAIDs** stimulate non-amyloidogenic APP processing in vitro.

DETD Cultured astrocytes or neurons are treated with aspirin or **resveratrol** for 1 h (at nano- or micromolar range), and secretion of soluble APPs is measured by Western blot analysis. The increase in APPs secretion caused by aspirin or **resveratrol** is accompanied by decreased levels of cellular and amyloidogenic APP holoprotein (FIG. 16). Thus, **NSAIDs** appear to stimulate non-amyloidogenic APP processing in vitro.

L11 ANSWER 12 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB **Resveratrol**, a plant **antibiotic**, has been found to have anticancer activity and was recently reported to induce apoptosis in the myeloid leukemia line HL60 by the CD95-CD95 ligand pathway. However, many acute lymphoblastic leukemias (ALLs), particularly of B-lineage, are resistant to CD95-mediated apoptosis. Using leukemia lines derived from patients with pro-B t(4;11), pre-B, and T-cell ALL, we show in this report that **resveratrol** induces extensive apoptotic cell death not only in CD95-sensitive leukemia lines, but also in B-lineage leukemic cells that are resistant to CD95-signaling. Multiple dose treatments of the leukemic cells with 50 .mu.M **resveratrol** resulted in .gtoreq.80% cell death with no statistically significant cytotoxicity against normal peripheral blood mononuclear cells under identical conditions. **Resveratrol** treatment did not increase CD95 expression or trigger sensitivity to CD95-mediated apoptosis in the ALL lines. Inhibition of CD95-signaling with a CD95-specific antagonistic antibody indicated that CD95-CD95 ligand interactions were not involved in initiating **resveratrol**-induced apoptosis. However, in each ALL line, **resveratrol** induced progressive loss of mitochondrial membrane potential as measured by the dual emission pattern of the mitochondria-selective dye JC-1. The broad spectrum caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone failed to block the depolarization of mitochondrial membranes induced by **resveratrol**, further indicating that **resveratrol** action was independent of upstream caspase-8 activation via receptor ligation. However, increases in caspase-9 activity ranged from 4- to 9-fold in the eight cell lines after treatment with **resveratrol**. Taken together, these results point to a general mechanism of apoptosis induction by **resveratrol** in ALL cells that involves a mitochondria/caspase-9-specific pathway for the activation of the caspase cascade and is independent of CD95-signaling.

| | |
|---|---|
| ACCESSION NUMBER: | 2001:465872 CAPLUS |
| DOCUMENT NUMBER: | 135:236064 |
| TITLE: | Resveratrol induces extensive apoptosis by depolarizing mitochondrial membranes and activating caspase-9 in acute lymphoblastic leukemia cells |
| AUTHOR(S): | Dorrie, Jan; Gerauer, Harald; Wachter, Yvonne; Zunino, Susan J. |
| CORPORATE SOURCE: | Friedrich-Alexander University of Erlangen-Nurnberg, Erlangen, D91058, Germany |
| SOURCE: | Cancer Research (2001), 61(12), 4731-4739<br>CODEN: CNREA8; ISSN: 0008-5472 |
| PUBLISHER: | American Association for Cancer Research |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |
| REFERENCE COUNT: | 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT |

AB **Resveratrol**, a plant **antibiotic**, has been found to have anticancer activity and was recently reported to induce apoptosis in the myeloid leukemia line HL60 by the CD95-CD95 ligand pathway. However, many acute lymphoblastic leukemias (ALLs), particularly of B-lineage, are resistant to CD95-mediated apoptosis. Using leukemia lines derived from patients with pro-B t(4;11), pre-B, and T-cell ALL, we show in this report that **resveratrol** induces extensive apoptotic cell death not only in CD95-sensitive leukemia lines, but also in B-lineage leukemic cells that are resistant to CD95-signaling. Multiple dose treatments of the leukemic cells with 50 .mu.M **resveratrol** resulted in .gtoreq.80% cell death with no statistically significant cytotoxicity against normal peripheral blood mononuclear cells under identical conditions. **Resveratrol** treatment did not increase CD95 expression or trigger sensitivity to CD95-mediated apoptosis in the ALL lines. Inhibition of CD95-signaling with a CD95-specific antagonistic antibody indicated that CD95-CD95 ligand interactions were not involved in initiating **resveratrol**-induced apoptosis. However, in each ALL line, **resveratrol** induced progressive loss of mitochondrial membrane potential as measured by the dual emission pattern of the mitochondria-selective dye JC-1. The broad spectrum caspase inhibitor benzyloxycarbonyl-Val-Ala-Asp-fluoromethylketone failed to block the depolarization of mitochondrial membranes induced by **resveratrol** , further indicating that **resveratrol** action was independent of upstream caspase-8 activation via receptor ligation. However, increases in caspase-9 activity ranged from 4- to 9-fold in the eight cell lines after treatment with **resveratrol**. Taken together, these results point to a general mechanism of apoptosis induction by **resveratrol** in ALL cells that involves a mitochondria/caspase-9-specific pathway for the activation of the caspase cascade and is independent of CD95-signaling.

L11 ANSWER 13 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB A review with 58 refs. **Resveratrol**, a naturally occurring **antibiotic** derived from plants, has been the focus of a no. of studies investigating its biol. attributes, which include antioxidant activity, anti-platelet-aggregation effects, antiatherogenic properties, an estrogen-like growth-promoting effect, growth-inhibiting activity, immunomodulation, and tumor chemoprevention. More recently, since the 1st report of the apoptosis-inducing activity of **resveratrol** in human cancer cells, the interest in this mol. as a potential chemotherapy agent has intensified. Not only has its role as an anticancer agent been corroborated, but the precise mechanism(s) of its anticancer activity is/are being elucidated. The cross-talk between the caspase family of proteases and mitochondria, in drug-induced apoptosis, has been studied. In this regard, the cancer-inhibitory activity of **resveratrol** may be attributable to its ability to trigger apoptosis in human leukemia and breast carcinoma cells. The cytotoxicity of **resveratrol** is restricted to these transformed cell types due to its ability to selectively upregulate CD95-CD95L interaction on the tumor cell surface, unlike the effects in normal peripheral blood cells. Despite the involvement of the CD95 signaling pathway, apoptosis induced by **resveratrol** is not accompanied by robust caspase 8 activation but involves mitochondrial release of cytochrome c and downstream activation of caspases 9 and 3. These in vitro findings have been extrapolated to a murine model of carcinogenesis, which demonstrated in vivo induction of apoptosis in mouse skin papillomas by the drug. These findings highlight the cancer-chemotherapeutic potential of this polyphenolic compd.

ACCESSION NUMBER: 2001:304072 CAPLUS

DOCUMENT NUMBER: 135:235646
TITLE: Resveratrol -- from the bottle to the bedside?
AUTHOR(S): Pervaiz, Shazib
CORPORATE SOURCE: Department of Physiology, National University of Singapore, Singapore, 119260, Singapore
SOURCE: Leukemia & Lymphoma (2001), 40(5/6), 491-498
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 58 refs. **Resveratrol**, a naturally occurring **antibiotic** derived from plants, has been the focus of a no. of studies investigating its biol. attributes, which include antioxidant activity, anti-platelet-aggregation effects, antiatherogenic properties, an estrogen-like growth-promoting effect, growth-inhibiting activity, immunomodulation, and tumor chemoprevention. More recently, since the 1st report of the apoptosis-inducing activity of **resveratrol** in human cancer cells, the interest in this mol. as a potential chemotherapy agent has intensified. Not only has its role as an anticancer agent been corroborated, but the precise mechanism(s) of its anticancer activity is/are being elucidated. The cross-talk between the caspase family of proteases and mitochondria, in drug-induced apoptosis, has been studied. In this regard, the cancer-inhibitory activity of **resveratrol** may be attributable to its ability to trigger apoptosis in human leukemia and breast carcinoma cells. The cytotoxicity of **resveratrol** is restricted to these transformed cell types due to its ability to selectively upregulate CD95-CD95L interaction on the tumor cell surface, unlike the effects in normal peripheral blood cells. Despite the involvement of the CD95 signaling pathway, apoptosis induced by **resveratrol** is not accompanied by robust caspase 8 activation but involves mitochondrial release of cytochrome c and downstream activation of caspases 9 and 3. These in vitro findings have been extrapolated to a murine model of carcinogenesis, which demonstrated in vivo induction of apoptosis in mouse skin papillomas by the drug. These findings highlight the cancer-chemotherapeutic potential of this polyphenolic compd.

L11 ANSWER 14 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB Prostaglandins (PG) derived from COX-1 are essential for the maintenance of mucosal integrity but COX-2 isoform synthesizes PG at a site of inflammation. Recently, COX-2 mRNA expression was demonstrated at the ulcer edge during healing of chronic gastric ulcers but the role for expression of COX-2 and its products such as PGE2 and cytokines including interleukin (IL-1.beta.) and tumor necrosis factor alpha (TNF.alpha.) in ulcer healing remains unknown. In this study, Wistar rats with gastric ulcers produced by serosal application of acetic acid (ulcer area 28 mm2) received daily treatment either with: (1) vehicle (saline); (2) NS-398 (10 mg/kg-d i.g.) and Vioxx (5 mg/kg-d i.g.), both, highly specific COX-2 inhibitors; (3) meloxicam (5 mg/kg-d i.g.), a preferential inhibitor of COX-2; (4) **resveratrol** (10 mg/kg-d i.g.), a specific COX-1 inhibitor; (5) indomethacin (5 mg/kg-d i.g); and (6) aspirin (ASA; 50 mg/kg-d i.g.), non-selective inhibitors of both COX-1 and COX-2. At day 3, 7, and 14 after ulcer induction, the animals were sacrificed and the area of gastric ulcers was detd. by planimetry and histol., gastric blood flow (GBF) at ulcer base and margin was measured by H2 clearance technique, and blood was withdrawn for measurement of plasma IL-1.beta. and TNF-.alpha. levels. The mucosal biopsy samples were taken for the

detn. of PGE2 generation by RIA and expression of COX-1, COX-2, IL-1.beta., and TNF.alpha. mRNA by RT-PCR. In vehicle-treated rats, gastric ulcers healed progressively and at day 14 the healing was completed, accompanied by a significant rise in the GBF at ulcer margin. The IL-1.beta., TNF.alpha., and COX-1 mRNA were detected in intact and ulcerated gastric mucosa, whereas COX-2 mRNA were upregulated only in ulcerated mucosa with peak obsd. at day 3 after ulcer induction. The plasma IL-1.beta. level was significantly increased at day 3 and 7 but then declined at day 14 to that measured in vehicle-controls. Indomethacin and ASA, which suppressed PGE2 generation both in the non-ulcerated and ulcerated gastric mucosa, significantly delayed the rate of ulcer healing and this was accompanied by the fall in GBF at ulcer margin and further elevation of plasma IL-1.beta. and TNF.alpha. levels, which was sustained up to the end of the study. Treatment with NS-398 and Vioxx, which caused only a moderate decrease in the PGE2 generation in the non-ulcerated gastric mucosa, delayed ulcer healing and attenuated significantly the GBF at ulcer margin and PGE2 generation in the ulcerated tissue, while raising the plasma IL-1.beta. and TNF.alpha. similarly to those obsd. in indomethacin- and ASA-treated rats. **Resveratrol**, which suppressed the PGE2 generation in both non-ulcerated and ulcerated gastric mucosa, prolonged ulcer healing and this was accompanied by the fall in the GBF at the ulcer margin and a significant increase in plasma IL-1.beta. and TNF.alpha. levels. We conclude that (1) classic **NSAID** delay ulcer healing due to suppression of endogenous PG, impairment in GBF at ulcer area, and excessive cytokine expression and release, and (2) this deleterious effect of classic **NSAID** on the healing of pre-existing ulcers can be reproduced by selective COX-1 and COX-2 inhibitors, suggesting that both COX isoforms are important sources of PG that appear to contribute to ulcer healing.

ACCESSION NUMBER: 2001:466317 CAPLUS
DOCUMENT NUMBER: 136:210224
TITLE: Classic NSAID and selective cyclooxygenase (COX)-1 and COX-2 inhibitors in healing of chronic gastric ulcers
AUTHOR(S): Brzozowski, Tomasz; Konturek, Peter C.; Konturek, Stanislaw J.; Sliwowski, Zbigniew; Pajdo, Robert; Drozdowicz, Danuta; Ptak, Agata; Hahn, Eckhart G.
CORPORATE SOURCE: Department of Physiology, Jagellonian University School of Medicine, Krakow, 31-531, Pol.
SOURCE: Microscopy Research and Technique (2001), 53(5), 343-353
CODEN: MRTEEO; ISSN: 1059-910X
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Prostaglandins (PG) derived from COX-1 are essential for the maintenance of mucosal integrity but COX-2 isoform synthesizes PG at a site of inflammation. Recently, COX-2 mRNA expression was demonstrated at the ulcer edge during healing of chronic gastric ulcers but the role for expression of COX-2 and its products such as PGE2 and cytokines including interleukin (IL-1.beta.) and tumor necrosis factor alpha (TNF.alpha.) in ulcer healing remains unknown. In this study, Wistar rats with gastric ulcers produced by serosal application of acetic acid (ulcer area 28 mm2) received daily treatment either with: (1) vehicle (saline); (2) NS-398 (10 mg/kg-d i.g.) and Vioxx (5 mg/kg-d i.g.), both, highly specific COX-2 inhibitors; (3) meloxicam (5 mg/kg-d i.g.), a preferential inhibitor of COX-2; (4) **resveratrol** (10 mg/kg-d i.g.), a specific COX-1

inhibitor; (5) indomethacin (5 mg/kg-d i.g); and (6) aspirin (ASA; 50 mg/kg-d i.g.), non-selective inhibitors of both COX-1 and COX-2. At day 3, 7, and 14 after ulcer induction, the animals were sacrificed and the area of gastric ulcers was detd. by planimetry and histol., gastric blood flow (GBF) at ulcer base and margin was measured by H2 clearance technique, and blood was withdrawn for measurement of plasma IL-1.beta. and TNF-.alpha. levels. The mucosal biopsy samples were taken for the detn. of PGE2 generation by RIA and expression of COX-1, COX-2, IL-1.beta., and TNF.alpha. mRNA by RT-PCR. In vehicle-treated rats, gastric ulcers healed progressively and at day 14 the healing was completed, accompanied by a significant rise in the GBF at ulcer margin. The IL-1.beta., TNF.alpha., and COX-1 mRNA were detected in intact and ulcerated gastric mucosa, whereas COX-2 mRNA were upregulated only in ulcerated mucosa with peak obsd. at day 3 after ulcer induction. The plasma IL-1.beta. level was significantly increased at day 3 and 7 but then declined at day 14 to that measured in vehicle-controls. Indomethacin and ASA, which suppressed PGE2 generation both in the non-ulcerated and ulcerated gastric mucosa, significantly delayed the rate of ulcer healing and this was accompanied by the fall in GBF at ulcer margin and further elevation of plasma IL-1.beta. and TNF.alpha. levels, which was sustained up to the end of the study. Treatment with NS-398 and Vioxx, which caused only a moderate decrease in the PGE2 generation in the non-ulcerated gastric mucosa, delayed ulcer healing and attenuated significantly the GBF at ulcer margin and PGE2 generation in the ulcerated tissue, while raising the plasma IL-1.beta. and TNF.alpha. similarly to those obsd. in indomethacin- and ASA-treated rats. **Resveratrol**, which suppressed the PGE2 generation in both non-ulcerated and ulcerated gastric mucosa, prolonged ulcer healing and this was accompanied by the fall in the GBF at the ulcer margin and a significant increase in plasma IL-1.beta. and TNF.alpha. levels. We conclude that (1) classic **NSAID** delay ulcer healing due to suppression of endogenous PG, impairment in GBF at ulcer area, and excessive cytokine expression and release, and (2) this deleterious effect of classic **NSAID** on the healing of pre-existing ulcers can be reproduced by selective COX-1 and COX-2 inhibitors, suggesting that both COX isoforms are important sources of PG that appear to contribute to ulcer healing.

IT 50-78-2, Aspirin 53-86-1, Indomethacin **501-36-0**, **Resveratrol** 71125-38-7, Meloxicam 123653-11-2, NS-398 162011-90-7, Vioxx
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(classic **NSAID** and selective cyclooxygenase (COX)-1 and COX-2 inhibitors in healing of chronic gastric ulcers)

L11 ANSWER 15 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB A beauty food is provided to have the excellent **antibiotic** effect and the inflammation repressing efficiency for the Propionibacterium acne known as a cause germ of a pimple. The compn. of the beauty food contains more than two Platycodi radix exts. among: the cortex acanthopanacis itself; or the **resveratrol** of the cortex acanthopanacis, the semen coicis, the ginkgo leaves ext., the alliin, the semen mungo ext., the grape juice and so on; or the red grape juice contg. the **resveratrol**, the polyphenol, and the anthocyanin. The compn. of the beauty food is produced by: extg. the material by an alc. according to the phys. chem. characteristic of a valid component; using by removing a fat-sol. material by a non-polar org. solvent after extg. by purified water; or mixing by directly adding.

ACCESSION NUMBER: 2001:888974 CAPLUS

DOCUMENT NUMBER: 135:370989
TITLE: Composition of beauty food and production method thereof
INVENTOR(S): Kang, Sang Mo
PATENT ASSIGNEE(S): S. Korea
SOURCE: Repub. Korean Kongkae Taeho Kongbo, No pp. given
CODEN: KRXXA7
DOCUMENT TYPE: Patent
LANGUAGE: Korean
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| KR 2000009820 | A | 20000215 | KR 1998-30458 | 19980729 |

AB A beauty food is provided to have the excellent **antibiotic** effect and the inflammation repressing efficiency for the Propionibacterium acne known as a cause germ of a pimple. The compn. of the beauty food contains more than two Platycodi radix exts. among: the cortex acanthopanacis itself; or the **resveratrol** of the cortex acanthopanacis, the semen coicis, the ginkgo leaves ext., the alliin, the semen mungo ext., the grape juice and so on; or the red grape juice contg. the **resveratrol**, the polyphenol, and the anthocyanin. The compn. of the beauty food is produced by: extg. the material by an alc. according to the phys. chem. characteristic of a valid component; using by removing a fat-sol. material by a non-polar org. solvent after extg. by purified water; or mixing by directly adding.

L11 ANSWER 16 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB This paper reports the functional characterization of AtrBp, an ABC transporter from Aspergillus nidulans. AtrBp is a multidrug transporter and has affinity to substrates belonging to all major classes of agricultural fungicides and some natural toxic compds. The substrate profile of AtrBp was detd. by assessing the sensitivity of deletion and overexpression mutants of atrB to several toxicants. All mutants showed normal growth as compared to control isolates. .DELTA.AtrB mutants displayed increased sensitivity to anilinopyrimidine, benzimidazole, phenylpyrrole, phenylpyridylamine, strobirulin and some azole fungicides. Increased sensitivity to the natural toxic compds. camptothecin (alkaloid), the phytoalexin **resveratrol** (stilbene) and the mutagen 4-nitroquinoline oxide was also found. Overexpression mutants were less sensitive to a wide range of chems. In addn. to the compds. mentioned above, decreased sensitivity to a broader range of azoles, dicarboximides, quintozene, acriflavine and rhodamine 6G was obsd. Decreased sensitivity in overexpression mutants neg. correlated with levels of atrB expression. The overexpression mutants displayed increased sensitivity to dithiocarbamate fungicides, chlorothalonil and the iron-activated **antibiotic** phleomycin. Accumulation of the azole fungicide [14C]fenarimol by the overexpression mutants was lower as compared to the parental isolate, demonstrating that AtrBp acts by preventing intracellular accumulation of the toxicant. Various metabolic inhibitors increased accumulation levels of [14C]fenarimol in the overexpression mutants to wild-type levels, indicating that reduced accumulation of the fungicide in these mutants is due to increased energy-dependent efflux as a result of higher pump capacity of AtrBp.
ACCESSION NUMBER: 2000:603539 CAPLUS
DOCUMENT NUMBER: 133:293383
TITLE: The ABC transporter AtrB from Aspergillus nidulans

mediates resistance to all major classes of fungicides and some natural toxic compounds

AUTHOR(S): Andrade, Alan C.; Del Sorbo, Giovanni; Van Nistelrooy, Johannes G. M.; De Waard, Maarten A.

CORPORATE SOURCE: Laboratory of Phytopathology, Wageningen University, Wageningen, 6700 EE, Neth.

SOURCE: Microbiology (Reading, United Kingdom) (2000), 146(8), 1987-1997
CODEN: MROBEO; ISSN: 1350-0872

PUBLISHER: Society for General Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB This paper reports the functional characterization of AtrBp, an ABC transporter from Aspergillus nidulans. AtrBp is a multidrug transporter and has affinity to substrates belonging to all major classes of agricultural fungicides and some natural toxic compds. The substrate profile of AtrBp was detd. by assessing the sensitivity of deletion and overexpression mutants of atrB to several toxicants. All mutants showed normal growth as compared to control isolates. .DELTA.AtrB mutants displayed increased sensitivity to anilinopyrimidine, benzimidazole, phenylpyrrole, phenylpyridylamine, strobirulin and some azole fungicides. Increased sensitivity to the natural toxic compds. camptothecin (alkaloid), the phytoalexin **resveratrol** (stilbene) and the mutagen 4-nitroquinoline oxide was also found. Overexpression mutants were less sensitive to a wide range of chems. In addn. to the compds. mentioned above, decreased sensitivity to a broader range of azoles, dicarboximides, quintozene, acriflavine and rhodamine 6G was obsd. Decreased sensitivity in overexpression mutants neg. correlated with levels of atrB expression. The overexpression mutants displayed increased sensitivity to dithiocarbamate fungicides, chlorothalonil and the iron-activated **antibiotic** phleomycin. Accumulation of the azole fungicide [14C]fenarimol by the overexpression mutants was lower as compared to the parental isolate, demonstrating that AtrBp acts by preventing intracellular accumulation of the toxicant. Various metabolic inhibitors increased accumulation levels of [14C]fenarimol in the overexpression mutants to wild-type levels, indicating that reduced accumulation of the fungicide in these mutants is due to increased energy-dependent efflux as a result of higher pump capacity of AtrBp.

L11 ANSWER 17 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB We and others previously showed that both the synthesis of the amyloid precursor protein (APP) and its processing (i.e., to amyloidogenic A.beta. peptides; sol. nonamyloidogenic APPs; and other APP fragments) are regulated by neurotransmitters. Transmitters that elevate cellular cAMP levels (like norepinephrine and prostaglandins, which act on .beta.-adrenergic receptors and prostaglandin E2 receptors resp.) enhance APP synthesis and the formation of amyloidogenic APP holoprotein. Transmitters that stimulate phosphatidylinositol hydrolysis (by activating muscarinic m1 or m3 receptors, serotoninergic 5HT2a or 5HT2c receptors, or metabotropic glutamate receptors of subtypes 1 or 5) increase the conversion of APP to sol. APPs, and decrease the formation of A.beta.. These findings suggest that drugs that regulate the activity of neurotransmitter receptors might be useful in preventing the excessive formation of A.beta. or other amyloid precursors in Alzheimer's disease. We now show that neuroimmunophilin ligands (like cyclosporin A or FK-506) and nonsteroidal antiinflammatory agents (NSAIDs), including

cyclooxygenase (COX)-2 inhibitors, can also prevent APP overexpression and the overprodn. of amyloidogenic peptides. We observe that the enhancement of APP overexpression by prostaglandin E2 is inhibited by neuroimmunophilin ligands like cyclosporin A or FK-506 (tacrolimus). We also find that the NSAIDs, which reduce prostaglandin synthesis by inhibiting COX-1 and -2 enzymes, might also be expected to lower APP levels. Our present data confirm that these drugs, as well as drugs that selectively inhibit COX-2, reduce the levels of amyloidogenic APP holoprotein in cultured neurons or in cultured astrocytes. We previously showed that elevations in cAMP, perhaps generated in response to prostaglandins, can suppress APPs secretion. The NSAIDs and COX inhibitors also increased levels of sol. APPs in the media of cultured astrocytes and neurons, perhaps acting by inhibition of prostaglandin prodn. Since APP holoprotein can be amyloidogenic, while APPs may be neurotrophic, our findings suggest that some neuroimmunophilin ligands, NSAIDs and COX-2 inhibitors might suppress amyloid formation and enhance neuronal regeneration in Alzheimer's disease.

ACCESSION NUMBER: 2001:83218 CAPLUS
DOCUMENT NUMBER: 135:102424
TITLE: Regulation of APP synthesis and secretion by neuroimmunophilin ligands and cyclooxygenase inhibitors
AUTHOR(S): Lee, Robert K. K.; Wurtman, Richard J.
CORPORATE SOURCE: Division of Health Sciences and Technology, Harvard University-Massachusetts Institute of Technology, Cambridge, MA, 02139, USA
SOURCE: Annals of the New York Academy of Sciences (2000), 920(Molecular Basis of Dementia), 261-268
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 50-78-2, Aspirin **501-36-0**, **Resveratrol** 59865-13-3, Cyclosporin A 104987-11-3, FK-506 178402-36-3, DFU 189954-66-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(regulation of APP synthesis and secretion by neuroimmunophilin ligands and **NSAIDs**, including cyclooxygenase inhibitors)

L11 ANSWER 18 OF 24 CAPLUS COPYRIGHT 2002 ACS
AB A review with 274 refs. The involvement of prostaglandins (PGs) and other eicosanoids in the development of human cancer has been known for over two decades. Importantly, an increase in PG synthesis may influence tumor growth in human beings and exptl. animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen metab., tumor cell proliferation and metastatic potential. PGs produced by cyclooxygenases (COXs) are represented by a large series of compds. that mainly enhance cancer development and progression, acting as carcinogens or tumor promoters, with profound effects on carcinogenesis. Further investigations suggest that arachidonic acid (AA) metabolites derived from lipoxygenase (LOX) pathways play an important role in growth-related signal transduction, implying that intervention through these pathways should be useful for arresting cancer progression. We discuss here the implications of COX and LOX in colon, pancreatic, breast, prostate, lung, skin, urinary bladder and liver cancers. Select inhibitors of COX and LOX

are described, including nonsteroidal antiinflammatory drugs ( **NSAIDs**), selective COX-2 inhibitors, curcumin, tea, silymarin and **resveratrol**, as well as a method useful for evaluating inhibitors of COX. Although a substantial amt. of addnl. work is required to yield a better understanding of the role of COX and LOX in cancer chemoprevention, it is clear that beneficial therapeutic effects can be realized through drug-mediated modulation of these metabolic pathways.

ACCESSION NUMBER: 2001:26538 CAPLUS
DOCUMENT NUMBER: 134:231402
TITLE: The role of cyclooxygenase and lipoxygenase in cancer chemoprevention
AUTHOR(S): Cuendet, Muriel; Pezzuto, John M.
CORPORATE SOURCE: Program for Collaborative Research in Pharmaceutical Sciences and Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, IL, 60612, USA
SOURCE: Drug Metabolism and Drug Interactions (2000), 17(1-4), 109-157
CODEN: DMDIEQ; ISSN: 0792-5077
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
REFERENCE COUNT: 274 THERE ARE 274 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB A review with 274 refs. The involvement of prostaglandins (PGs) and other eicosanoids in the development of human cancer has been known for over two decades. Importantly, an increase in PG synthesis may influence tumor growth in human beings and exptl. animals, and numerous studies have illustrated the effect of PG synthesis on carcinogen metab., tumor cell proliferation and metastatic potential. PGs produced by cyclooxygenases (COXs) are represented by a large series of compds. that mainly enhance cancer development and progression, acting as carcinogens or tumor promoters, with profound effects on carcinogenesis. Further investigations suggest that arachidonic acid (AA) metabolites derived from lipoxygenase (LOX) pathways play an important role in growth-related signal transduction, implying that intervention through these pathways should be useful for arresting cancer progression. We discuss here the implications of COX and LOX in colon, pancreatic, breast, prostate, lung, skin, urinary bladder and liver cancers. Select inhibitors of COX and LOX are described, including nonsteroidal antiinflammatory drugs ( **NSAIDs**), selective COX-2 inhibitors, curcumin, tea, silymarin and **resveratrol**, as well as a method useful for evaluating inhibitors of COX. Although a substantial amt. of addnl. work is required to yield a better understanding of the role of COX and LOX in cancer chemoprevention, it is clear that beneficial therapeutic effects can be realized through drug-mediated modulation of these metabolic pathways.

L11 ANSWER 19 OF 24 USPATFULL

AB A composition and method of cancer chemoprevention is disclosed. The composition and method utilize resveratrol as a cancer chemopreventative agent in mammals, including humans.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 1999:170652 USPATFULL
TITLE: Cancer chemopreventative composition and method
INVENTOR(S): Pezzuto, John M., River Forest, IL, United States
Moon, Richard C., Plant City, FL, United States

| | |
|---|---|
| PATENT ASSIGNEE(S): | Jang, Mei-Shiang, Chicago, IL, United States<br>Pharmascience, Quebec, Canada (non-U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6008260 | | 19991228 |
| APPLICATION INFO.: | US 1998-5114 | | 19980109 (9) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Goldberg, Jerome D. |
| LEGAL REPRESENTATIVE: | Marshall, O'Toole, Gerstein, Murray & Borun |
| NUMBER OF CLAIMS: | 16 |
| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 5 Drawing Figure(s); 3 Drawing Page(s) |
| LINE COUNT: | 577 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD **Resveratrol** was found to inhibit cellular events associated with tumor initiation, promotion, and progression. As discussed hereafter, the activity of **resveratrol** was demonstrated on the basis of ability of **resveratrol** to inhibit the cyclooxygenase activity of COX-1 (i.e., median effective dose ED.sub.50 of 15 .mu.M). This activity correlates with antitumor promotion. Although the inhibitory activity of **resveratrol** was less than that of some **NSAIDs**, such as indomethacin (ED.sub.50 =2.3 .mu.M), the **resveratrol** activity was much greater than the activity of compounds such as aspirin (ED.sub.50 =880 .mu.M). Also, unlike indomethacin and most other **NSAIDs**, **resveratrol** inhibited the hydroperoxidase activity of COX-1 (ED.sub.50 =3.7 .mu.M).

L11 ANSWER 20 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB **Resveratrol** and quercetin are polyphenols which have been detected in significant amts. in green vegetables, citrus fruits and red grape wines. Beneficial effects attributed to these compds. include anti-inflammatory, antiviral and antitumor properties. The effect of **resveratrol** and quercetin on growth of human oral cancer cells is unknown. **Resveratrol** and quercetin, in concns. of 1 to 100 .mu.M, were incubated in triplicates with human oral squamous carcinoma cells SCC-25 in DMEM-HAM's F-12 supplemented with fetal calf serum and **antibiotics** in an atm. of 5% CO2 in air at 37.degree.C for 72 h. Cell growth was detd. by counting the no. of viable cells with a hemocytometer. Cell proliferation was measured by means of incorporation of [3H]thymidine in nuclear DNA. **Resveratrol** at 10 and 100 .mu.M induced significant dose-dependent inhibition in cell growth as well as in DNA synthesis. Quercetin exhibited a biphasic effect, stimulation at 1 and 10 .mu.M, and minimal inhibition at 100 .mu.M in cell growth and DNA synthesis. Combining 50 .mu.M of **resveratrol** with 10, 25 and 50 .mu.M of quercetin resulted in a gradual and significant increase in the inhibitory effect of quercetin on cell growth and DNA synthesis. We conclude that **resveratrol** or a combination of **resveratrol** and quercetin, in concns. equiv. to that present in red wines, are effective inhibitors of oral squamous carcinoma cell (SCC-25) growth and proliferation, and warrant further investigation as cancer chemopreventive agents.

| | |
|---|---|
| ACCESSION NUMBER: | 1999:288549 CAPLUS |
| DOCUMENT NUMBER: | 131:67783 |
| TITLE: | Modulating effect of resveratrol and quercetin on oral cancer cell growth and proliferation |
| AUTHOR(S): | ElAttar, Tawfik M. A.; Virji, Adi S. |

CORPORATE SOURCE: Hormone Research Laboratory, Schools of Dentistry and Medicine, University of Missouri-Kansas City, Kansas City, MI, 64108, USA
SOURCE: Anti-Cancer Drugs (1999), 10(2), 187-193
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB **Resveratrol** and quercetin are polyphenols which have been detected in significant amts. in green vegetables, citrus fruits and red grape wines. Beneficial effects attributed to these compds. include anti-inflammatory, antiviral and antitumor properties. The effect of **resveratrol** and quercetin on growth of human oral cancer cells is unknown. **Resveratrol** and quercetin, in concns. of 1 to 100 .mu.M, were incubated in triplicates with human oral squamous carcinoma cells SCC-25 in DMEM-HAM's F-12 supplemented with fetal calf serum and **antibiotics** in an atm. of 5% CO2 in air at 37.degree.C for 72 h. Cell growth was detd. by counting the no. of viable cells with a hemocytometer. Cell proliferation was measured by means of incorporation of [3H]thymidine in nuclear DNA. **Resveratrol** at 10 and 100 .mu.M induced significant dose-dependent inhibition in cell growth as well as in DNA synthesis. Quercetin exhibited a biphasic effect, stimulation at 1 and 10 .mu.M, and minimal inhibition at 100 .mu.M in cell growth and DNA synthesis. Combining 50 .mu.M of **resveratrol** with 10, 25 and 50 .mu.M of quercetin resulted in a gradual and significant increase in the inhibitory effect of quercetin on cell growth and DNA synthesis. We conclude that **resveratrol** or a combination of **resveratrol** and quercetin, in concns. equiv. to that present in red wines, are effective inhibitors of oral squamous carcinoma cell (SCC-25) growth and proliferation, and warrant further investigation as cancer chemopreventive agents.

L11 ANSWER 21 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB The ability of green tea components and other antioxidant compds. to function as antimutagens/antioxidants has been well established, and their role in cancer prevention is supported by numerous epidemiol. studies. We have utilized modified Ames tests, superoxide scavenging assays, and assays for protection against DNA scissions to compare and contrast the protective effects of various teas and com. and lab.-isolated tea components to those produced by compds. such as **resveratrol**, selenium, curcumin, vitamins C and E, quercetin dihydrate, sulforaphane, ellagic acid dihydrate, glutathione reduced, trolox, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and N-acetyl-L-cysteine (NAC). In Ames tests, employing hydrogen peroxide as a mutagen, epigallocatechin gallate (EGCG) produced the highest level of protection of all antioxidants tested. Measurement of protection against DNA scissions produced results that again showed that EGCG produced the strongest protective effects. In scavenging assays using a xanthine-xanthine oxidase (enzymic system), epicatechin gallate (ECG) showed the highest scavenging potential. In a nonenzymic (phenazine methosulfate-NADH) oxidizing system, EGCG once again showed the strongest effects. The implications of these and similar results are discussed in relation to cancer prevention and prevention of drug/**antibiotic** resistance.

ACCESSION NUMBER: 1999:797459 CAPLUS
DOCUMENT NUMBER: 132:246306

09/694,108

TITLE: Antimutagenic/antioxidant activity of green tea components and related compounds
AUTHOR(S): Pillai, Segaran P.; Mitscher, Lester A.; Menon, Sanjay R.; Pillai, Christine A.; Shankel, Delbert M.
CORPORATE SOURCE: Departments of Medicinal Chemistry and Molecular Bioscience, University of Kansas, Lawrence, KS, 66045, USA
SOURCE: Journal of Environmental Pathology, Toxicology and Oncology (1999), 18(3), 147-158
CODEN: JEPOEC; ISSN: 0731-8898
PUBLISHER: Begell House, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB The ability of green tea components and other antioxidant compds. to function as antimutagens/antioxidants has been well established, and their role in cancer prevention is supported by numerous epidemiol. studies. We have utilized modified Ames tests, superoxide scavenging assays, and assays for protection against DNA scissions to compare and contrast the protective effects of various teas and com. and lab.-isolated tea components to those produced by compds. such as **resveratrol**, selenium, curcumin, vitamins C and E, quercetin dihydrate, sulforaphane, ellagic acid dihydrate, glutathione reduced, trolox, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and N-acetyl-L-cysteine (NAC). In Ames tests, employing hydrogen peroxide as a mutagen, epigallocatechin gallate (EGCG) produced the highest level of protection of all antioxidants tested. Measurement of protection against DNA scissions produced results that again showed that EGCG produced the strongest protective effects. In scavenging assays using a xanthine-xanthine oxidase (enzymic system), epicatechin gallate (ECG) showed the highest scavenging potential. In a nonenzymic (phenazine methosulfate-NADH) oxidizing system, EGCG once again showed the strongest effects. The implications of these and similar results are discussed in relation to cancer prevention and prevention of drug/**antibiotic** resistance.

L11 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB **Resveratrol** and chalcone synthases are related plant-specific polyketide synthases that are key enzymes in the biosynthesis of stilbenes and flavonoids, resp. The stepwise condensing reactions correspond to those in other polyketide and fatty-acid synthases. This predicts that the two proteins also contain cysteines that are essential for enzyme activity because they bind the substrates. In both enzymes, all of the 6 conserved cysteines were changed to alanine by site-directed mutagenesis and the mutants were tested after expression of the proteins in the Escherichia coli heterologous system. Only cysteine 169 was essential in both enzymes, and inhibitor studies suggest that it is the main target of cerulenin, an **antibiotic** reacting with the cysteine in the active center of condensing enzymes. Most of the other exchanges led to reduced activities. In two cases, the enzymes responded differently, suggesting that the cysteines at positions 135 and 195 may be involved in the different product specificity of the two enzymes. The sequences surrounding the essential cysteine 169 revealed no similarity to the active sites of condensing enzymes in other polyketide synthases and in fatty acid biosynthesis. The available data indicate that **resveratrol** and chalcone synthases represent a group of enzymes that evolved independently of other condensing enzymes.

ACCESSION NUMBER: 1991:404096 CAPLUS
DOCUMENT NUMBER: 115:4096
TITLE: The role of cysteines in polyketide synthases. Site-directed mutagenesis of resveratrol and chalcone synthases, two key enzymes in different plant-specific pathways
AUTHOR(S): Lanz, Thomas; Tropf, Susanne; Marner, Franz Josef; Schroeder, Joachim; Schroeder, Gudrun
CORPORATE SOURCE: Inst. Biol. II, Univ. Freiburg, Freiburg, D-7800, Fed. Rep. Ger.
SOURCE: J. Biol. Chem. (1991), 266(15), 9971-6
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Resveratrol** and chalcone synthases are related plant-specific polyketide synthases that are key enzymes in the biosynthesis of stilbenes and flavonoids, resp. The stepwise condensing reactions correspond to those in other polyketide and fatty-acid synthases. This predicts that the two proteins also contain cysteines that are essential for enzyme activity because they bind the substrates. In both enzymes, all of the 6 conserved cysteines were changed to alanine by site-directed mutagenesis and the mutants were tested after expression of the proteins in the Escherichia coli heterologous system. Only cysteine 169 was essential in both enzymes, and inhibitor studies suggest that it is the main target of cerulenin, an **antibiotic** reacting with the cysteine in the active center of condensing enzymes. Most of the other exchanges led to reduced activities. In two cases, the enzymes responded differently, suggesting that the cysteines at positions 135 and 195 may be involved in the different product specificity of the two enzymes. The sequences surrounding the essential cysteine 169 revealed no similarity to the active sites of condensing enzymes in other polyketide synthases and in fatty acid biosynthesis. The available data indicate that **resveratrol** and chalcone synthases represent a group of enzymes that evolved independently of other condensing enzymes.

L11 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2002 ACS
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The chem. constituents of a Japanese sedge birodo-suge (C. fedia miyabei) were investigated, and four 3,5,4'-trihydroxystilbene (**resveratrol** ) oligomers (one dimer, one trimer, and two tetramers) were isolated. Their structures were detd. by spectroscopic evidence and biogenetic consideration. The dimer was identified as .epsilon.-viniferin that had already been identified as a phytoalexin of grape vine leaves. The trimer and the tetramers were structurally new compds., and were named miyabenols C (I) (for the trimer), and A (II) and B (III) (for the tetramers). The antimicrobial test of II (the predominant constituent) revealed that II was **antibiotic** only against gram-pos. bacteria.

ACCESSION NUMBER: 1987:474260 CAPLUS
DOCUMENT NUMBER: 107:74260
TITLE: New 3,5,4'-trihydroxystilbene (resveratrol) oligomers from Carex fedia Nees var. miyabei (Franchet) T. Koyama (Cyperaceae)

AUTHOR(S): Suzuki, Ken; Shimizu, Tomoko; Kawabata, Jun; Mizutani, Junya
CORPORATE SOURCE: Fac. Agric., Hokkaido Univ., Sapporo, 060, Japan
SOURCE: Agric. Biol. Chem. (1987), 51(4), 1003-8
CODEN: ABCHA6; ISSN: 0002-1369
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chem. constituents of a Japanese sedge birodo-suge (C. fedia miyabei) were investigated, and four 3,5,4'-trihydroxystilbene (**resveratrol**) oligomers (one dimer, one trimer, and two tetramers) were isolated. Their structures were detd. by spectroscopic evidence and biogenetic consideration. The dimer was identified as .epsilon.-viniferin that had already been identified as a phytoalexin of grape vine leaves. The trimer and the tetramers were structurally new compds., and were named miyabenols C (I) (for the trimer), and A (II) and B (III) (for the tetramers). The antimicrobial test of II (the predominant constituent) revealed that II was **antibiotic** only against gram-pos. bacteria.

ST Carex **resveratrol** oligomer; miyabenol Carex; **antibiotic** miyabenol A Carex

L11 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2002 ACS

AB The **antibiotic** activities of exts. of Gnetum paniculatum and G. schwackeanum and of substances isolated from the latter plant, namely **resveratrol**, gnetin C, and gnetin E, were tested against several bacteria and fungi. The ext. and all the substances isolated from G. schwackeanum were active toward Staphylococcus aureus, S. epidermis and Mycobacterium sme gamatis. Gnetin C and **resveratrol** showed activity against Mycobacterium albicans, but only gnetin C was active toward C. parapsilosis and Saccharomyces cerevisiae.

ACCESSION NUMBER: 1988:17670 CAPLUS
DOCUMENT NUMBER: 108:17670
TITLE: Antibacteria and antifungal activity of Gnetum compounds
AUTHOR(S): Giesbrecht, Astrea M.; Purchio, Adhemar; Ujikama, Keidi; Ribeiro, Maria N. S.
CORPORATE SOURCE: Inst. Cienc. Biomed., Univ. Sao Paulo, Sao Paulo, Brazil
SOURCE: Acta Amazonica (1985), 15(3-4), 321-5
CODEN: AAMZAZ; ISSN: 0044-5967
DOCUMENT TYPE: Journal
LANGUAGE: Portuguese

AB The **antibiotic** activities of exts. of Gnetum paniculatum and G. schwackeanum and of substances isolated from the latter plant, namely **resveratrol**, gnetin C, and gnetin E, were tested against several bacteria and fungi. The ext. and all the substances isolated from G. schwackeanum were active toward Staphylococcus aureus, S. epidermis and Mycobacterium sme gamatis. Gnetin C and **resveratrol** showed activity against Mycobacterium albicans, but only gnetin C was active toward C. parapsilosis and Saccharomyces cerevisiae.

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     (FILE 'HOME' ENTERED AT 20:15:59 ON 11 JUL 2002)

     FILE 'REGISTRY' ENTERED AT 20:16:18 ON 11 JUL 2002
               E RESVERATROL/CN
L1             1 S E3

     FILE 'STNGUIDE' ENTERED AT 20:17:20 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:24:43 ON 11 JUL 2002
L2          1307 S (L1 OR RESVERATROL?)
L3             7 S L2 AND RESPIRAT? AND INFLAMMAT? AND (ASTHMA? OR ALVEOLITI? OR
L4             7 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 20:36:40 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:40:02 ON 11 JUL 2002
L5            16 S L2 AND (ASTHMA? OR ALVEOLITI? OR COPD OR CHRONIC(2A)OBSTRUCT?
L6            15 DUP REM L5 (1 DUPLICATE REMOVED)
L7             8 S L6 NOT L3

     FILE 'STNGUIDE' ENTERED AT 20:45:33 ON 11 JUL 2002

     FILE 'STNGUIDE' ENTERED AT 20:56:41 ON 11 JUL 2002

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=> e resveratrol/cn
E1            1     RESUSCITATION-PROMOTING FACTOR PROTEIN (MICROCOCCUS LUTEUS S
                    TRAIN JCM-3348)/CN
E2            1     RESUSCITATION-PROMOTING FACTOR PROTEIN (MICROCOCCUS LUTEUS S
                    TRAIN NCIMB-13267)/CN
E3            1 --> RESVERATROL/CN
E4            1     RESVERATROL .BETA.-D-GLUCOSIDE/CN
E5            1     RESVERATROL 12-C-.BETA.-GLUCOPYRANOSIDE/CN
E6            1     RESVERATROL 3-O-.BETA.-GLUCOPYRANOSIDE/CN
E7            1     RESVERATROL 4'-O-.BETA.-D-GLUCOPYRANOSIDE/CN
E8            1     RESVERATROL CIS-DEHYDRODIMER/CN
E9            1     RESVERATROL GLUCOSIDE/CN
E10           1     RESVERATROL SYNTHASE/CN
E11           1     RESVERATROL SYNTHASE (PEANUT)/CN
E12           1     RESVERATROL TRANS-DEHYDRODIMER/CN

=> s e3
L1            1 RESVERATROL/CN

=> d l1 1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2002 ACS
RN   501-36-0  REGISTRY
CN   1,3-Benzenediol, 5-[(1E)-2-(4-hydroxyphenyl)ethenyl]- (9CI)  (CA INDEX
     NAME)
OTHER CA INDEX NAMES:
CN   1,3-Benzenediol, 5-[2-(4-hydroxyphenyl)ethenyl]-, (E)-
CN   3,4',5-Stilbenetriol (7CI, 8CI)
CN   Resveratrol (6CI)
OTHER NAMES:
CN   (E)-5-(p-Hydroxystyryl)resorcinol
CN   (E)-Resveratrol
CN   3,5,4'-Trihydroxystilbene
CN   CA 1201
CN   trans-Resveratrol
FS   STEREOSEARCH
DR   31100-06-8
MF   C14 H12 O3
CI   COM
LC   STN Files:   ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*,
       BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAOLD, CAPLUS, CASREACT,
       CEN, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, HODOC*, IPA, MEDLINE,
       MRCK*, NAPRALERT, PHAR, PROMT, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)

Double bond geometry as shown.
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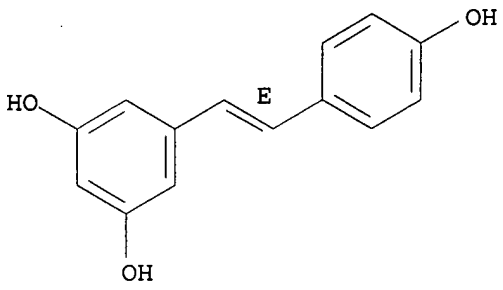


**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

944 REFERENCES IN FILE CA (1967 TO DATE)
40 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
953 REFERENCES IN FILE CAPLUS (1967 TO DATE)
10 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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FILE 'CAPLUS' ENTERED AT 20:24:43 ON 11 JUL 2002
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=> d his

     (FILE 'HOME' ENTERED AT 20:15:59 ON 11 JUL 2002)

     FILE 'REGISTRY' ENTERED AT 20:16:18 ON 11 JUL 2002
               E RESVERATROL/CN
L1             1 S E3

     FILE 'STNGUIDE' ENTERED AT 20:17:20 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:24:43 ON 11 JUL 2002

=> s (l1 or resveratrol?)
L2          1307 (L1 OR RESVERATROL?)

=> s l2 and respirat? and inflammat? and (asthma? or alveoliti? or copd or
chronic(2a)obstruct?(3a)pulmonary(2a)disease? or bronchit? or cystic(2a)fibro? or
bronchiecta? or interstitial(4a)lung)
L3             7 L2 AND RESPIRAT? AND INFLAMMAT? AND (ASTHMA? OR ALVEOLITI? OR
                 COPD OR CHRONIC(2A) OBSTRUCT?(3A) PULMONARY(2A) DISEASE? OR
                 BRONCHIT? OR CYSTIC(2A) FIBRO? OR BRONCHIECTA? OR INTERSTITIAL(4
                 A) LUNG)

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4             7 DUP REM L3 (0 DUPLICATES REMOVED)

=> d l4 abs ibib kwic 1-7

L4   ANSWER 1 OF 7  CAPLUS  COPYRIGHT 2002 ACS
AB   A method is provided for treating inflammatory
     respiratory disorders such as asthma and chronic
     obstructive pulmonary disease (COPD
     ). The method involves administration, preferably oral or pulmonary
     administration, of an active agent selected from the group consisting of
     resveratrol, pharmacol. acceptable salts, esters, amides, prodrugs
     and analogs thereof, and combinations of any of the foregoing.
     Pharmaceutical formulations for use in conjunction with the aforementioned
     method are provided as well.
ACCESSION NUMBER:         2002:314756  CAPLUS
DOCUMENT NUMBER:          136:319401
TITLE:                    Administration of resveratrol to treat
                          inflammatory respiratory disorders
INVENTOR(S):              Donnelly, Louise Elizabeth; Barnes, Peter John
PATENT ASSIGNEE(S):       Imperial College Innovations Limited, UK
SOURCE:                   PCT Int. Appl., 34 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
```

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002032410 | A2 | 20020425 | WO 2001-GB4672 | 20011019 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-694108 A 20001019

TI Administration of **resveratrol** to treat **inflammatory respiratory** disorders

AB A method is provided for treating **inflammatory respiratory** disorders such as **asthma** and **chronic obstructive pulmonary disease** (**COPD**). The method involves administration, preferably oral or pulmonary administration, of an active agent selected from the group consisting of **resveratrol**, pharmacol. acceptable salts, esters, amides, prodrugs and analogs thereof, and combinations of any of the foregoing. Pharmaceutical formulations for use in conjunction with the aforementioned method are provided as well.

ST **inflammatory respiratory** disorder **resveratrol**

IT Transcription factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(NF-.kappa.B (nuclear factor .kappa.B); **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Lung, disease
(**alveolitis**; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Lung
(alveolus; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Macrolides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antibiotics; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Occupational diseases
(**asthma**; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Bronchi
(chronic **bronchitis**; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Lung, disease
(chronic obstructive; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Gene, animal
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inflammatory**; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT Leukotriene receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(inhibitors; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Antibiotics
(macrolide; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Anti-**inflammatory** agents
(nonsteroidal; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT **Asthma**
(occupational; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Drug delivery systems
(oral; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Drug delivery systems
(parenterals; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Drug delivery systems
(pulmonary; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Antiasthmatics
**Asthma**
Bronchodilators
Concrete
Dust
Emphysema
Flours and Meals
Human
Tobacco smoke
Wood
(**resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Allergens
Asbestos
Bituminous coal
Clays, biological studies
Lime (chemical)
Polymers, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(**resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Interleukin 8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Glucocorticoids
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT Adrenoceptor agonists
(.beta.2-; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT 125978-95-2, Nitric oxide synthase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inducible; **resveratrol** treatment of **inflammatory** **respiratory** disorders)
IT 9040-59-9, Cyclic nucleotide phosphodiesterase

RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; **resveratrol** treatment of **inflammatory respiratory** disorders)

IT 57-50-1, Sugar, biological studies 7440-41-7, Beryllium, biological studies 7440-44-0, Carbon, biological studies 7631-86-9, Silica, biological studies 9004-34-6, Cellulose, biological studies 9005-25-8, Starch, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (**resveratrol** treatment of **inflammatory respiratory** disorders)

IT 83869-56-1, Granulocyte-macrophage colony-stimulating factor
RL: BSU (Biological study, unclassified); BIOL (Biological study) (**resveratrol** treatment of **inflammatory respiratory** disorders)

IT 50-02-2, Dexamethasone 50-23-7, Hydrocortisone 58-55-9, Theophylline, biological studies **501-36-0**, trans-**Resveratrol** 27208-80-6 51333-22-3, Budesonide 61434-67-1, cis-**Resveratrol** 94749-08-3, Salmeterol xinafoate 107032-81-5 148766-36-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**resveratrol** treatment of **inflammatory respiratory** disorders)

L4 ANSWER 2 OF 7 USPATFULL

AB Compositions and methods for the treatment of anorectal disorders are provided in which certain combinations of NO donors, PDE inhibitors, superoxide (O.sub.2.sup.-) scavengers, .beta.-adrenergic agonists, cAMP-dependent protein kinase activators, .alpha..sub.1-adrenergic antagonists, L-type Ca.sup.2+ channel blockers, estrogens, ATP-sensitive K.sup.+ channel activators and smooth muscle relaxants are used.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 2002:141535 USPATFULL |
| TITLE: | Compositions and methods for the treatment of anorectal disorders |
| INVENTOR(S): | Parks, Thomas P., San Mateo, CA, UNITED STATES<br>Mak, Vivien, Palo Alto, CA, UNITED STATES<br>Lee, Jung-Chung, Sunnyvale, CA, UNITED STATES<br>Lee, Charles, Union City, CA, UNITED STATES |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002072522 | A1 | 20020613 |
| APPLICATION INFO.: | US 2001-919590 | A1 | 20010730 (9) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-460306, filed on 13 Dec 1999, PENDING Continuation-in-part of Ser. No. US 2000-595390, filed on 14 Jun 2000, PENDING Continuation-in-part of Ser. No. US 2001-769621, filed on 23 Jan 2001, PENDING

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-222267P | 20000731 (60) |
| | US 1998-112325P | 19981214 (60) |
| | US 1999-139916P | 19990617 (60) |
| | US 1999-155318P | 19990921 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | APPLICATION |

09/694,108

LEGAL REPRESENTATIVE: TOWNSEND AND TOWNSEND AND CREW, LLP, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
NUMBER OF CLAIMS: 34
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 13 Drawing Page(s)
LINE COUNT: 2514
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . "signs and symptoms of anorectal disease" include, but are not limited to, anal sphincter hypertonicity; anal and rectal ischemia, itching, **inflammation**, pain or bleeding; thrombosed or prolapsed hemorrhoidal tissue; spasticity of the levator ani muscle, spasm of the puboretalis muscle or. . .

DETD . . . anal sphincter relaxation; reduction of anal sphincter pressure; maintenance of reduced anal sphincter pressure; reduction or elimination of ischemia, itching, **inflammation**, pain, bleeding, or muscle spasm; restoration or improvement of anoderm blood flow; dilation of blood vessels in the anus and. . .

DETD . . . to 17-beta-estrodiol, estrone, mestranol, estradiol valerate, estrodiol dypionate, ethinyl estrodiol, quinestrol, estrone sulfate, phytoestrogens such as flavones, isoflavones (e.g. genistein), **resveratrol**, coumestan derivatives, other synthetic estrogenic compounds including pesticides (e.g. p,p'-DDT), plasticizers (e.g. bisphenol A), and a variety of other industrial. . .

DETD . . . and salbutamol (albuterol) are .beta.2-adrenergic agonists commonly used for the long-term treatment of obstructive airway diseases and acute bronchospasm in **asthma**. Beta-adrenergic agents, like VIP, potently relax smooth muscle, including IAS smooth muscle by raising intracellular cyclic AMP levels (Parks et. . . leads to down-regulation of .beta. receptors in some tissues and decreased pharmacological responses, and has been demonstrated in patients with **asthma**.sup.1.

DETD . . . to 17-beta-estrodiol, estrone, mestranol, estradiol valerate, estrodiol dypionate, ethinyl estrodil, quinestrol, estrone sulfate, phytoestrogens such as flavones, isoflavones (e.g. genistein), **resveratrol**, coumestan derivatives, other synthetic estrogenic compounds including pesticides (e.g. p,p'-DDT), plasticizers (e.g. bisphenol A), and a variety of other industrial. . .

DETD [0167] Theophylline, a plant-derived methylxanthine, has been used for the treatment of bronchial **asthma** for decades. Theophylline relaxes smooth muscle, notably bronchial muscle, that has been contracted experimentally with a spasmogen, or clinically in **asthma**. We found that theophylline relaxed the rat IAS when instilled into the distal anal canal. Proposed mechanisms of methylxanthine-induced physiologic. . . doses.sup.2. .sup.2 Goodman & Gilman's "The Pharmacological Basis of Therapeutics" 9th edition. Chapter 28, Drugs Used in the Treatment of **Asthma**. William E. Serafin, 1996.

DETD . . . acceptable carrier and at least one of the following second pharmacologic agents: a local anesthetic (e.g., lidocaine, prilocaine, etc.), local anti-**inflammatory** agent (e.g., naproxen, pramoxicam, etc.), corticosteroid (e.g., cortisone, hydrocortisone, etc.), anti-itch agent (e.g., loperamide diphylenoxalate, etc.), an agent that interferes. . .

DETD . . . membrane and disintegrate and/or dissolve rapidly to allow immediate local and systemic absorption. These formulations are used along with the anti-**inflammatory** agents of the present invention for reducing or eliminating **inflammation** of transmucosal membranes.

DETD . . . the buccal mucosa, allows for controlled release of the pharmacological agent into the mouth and through the buccal mucosa. The anti-**inflammatory** agents of the present invention can be incorporated into these formulations as well.

DETD . . . solutions for creating aerosol inhalants is discussed in Remington's Pharmaceutical Sciences, see also, Ganderton and Jones, DRUG DELIVERY TO THE **RESPIRATORY** TRACT, Ellis Horwood (1987); Gonda (1990) Critical Reviews in Therapeutic Drug Carrier Systems 6:273-313; and Raeburn et al., (1992) J. . .

DETD [0206] Similarly, the invention provides methods of using the compositions above in combinations with local anti-**inflammatory** agents, for example, naproxen, piroxicam, etc. in a pharmaceutically acceptable dosage form as an effective treatment for a medical condition. . .

DETD . . . software. Blood pressure changes were monitored using an arterial catheter/transducer and a Digi-Med Blood Pressure Analyzer with the DMSI software. **Respiratory** changes were monitored using a mercury strain gauge/transducer, wrapped around the rib-cage of the rat, hooked up to a Digi-Med. . .

DETD . . . and 5) adenosine receptor antagonism (Goodman & Gilman's "The Pharmacological Basis of Therapeutics" 9.sup.th edition. Section IV-Autocoids; Drug Therapy of **Inflammation**).

L4 ANSWER 3 OF 7 USPATFULL

AB Disclosed are various controlled release pharmaceutical compositions that include an agent that enhances or modulates the endogenous production of nitric oxide in a mammal. Controlled release pharmaceutical compositions of L-arginine, its salts, peptides, and biological equivalents, together with methods of using the compositions are included. Also included are controlled release pharmaceutical compositions of botanical extracts that modulate or enhance the production of nitric oxide, either alone or in combination with L-arginine or its biological equivalent.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | | | |
|---|---|---|---|
| ACCESSION NUMBER: | 2002:133512 USPATFULL | | |
| TITLE: | CONTROLLED RELEASE NITRIC OXIDE PRODUCING AGENTS | | |
| INVENTOR(S): | KUHRTS, ERIC H., REDWOOD CITY, CA, UNITED STATES | | |
| | NUMBER | KIND | DATE |
| PATENT INFORMATION: | US 2002068365 | A1 | 20020606 |
| APPLICATION INFO.: | US 1998-123849 | A1 | 19980728 (9) |
| DOCUMENT TYPE: | Utility | | |
| FILE SEGMENT: | APPLICATION | | |
| LEGAL REPRESENTATIVE: | BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747 | | |
| NUMBER OF CLAIMS: | 25 | | |
| EXEMPLARY CLAIM: | 1 | | |
| LINE COUNT: | 862 | | |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . possible. For example, French maritime pine bark extract, a mixture of bioflavonoids, is known to modulate nitric oxide metabolism in **inflammation**. Ginkgo biloba and garlic are also known to regulate nitric oxide metabolism. Controlled release formulations of these botanical extracts would. . .

SUMM . . . bark extract, Henkel, Inc.), extracts of rosemary such as carnosol, botanical anti-oxidants such as green tea polyphenols, grape

seed extract, **resveratrol**, ginkgo biloba, and garlic extracts. Folic acid may also be added as the preferred vitamin.

SUMM . . . kidneys; cardiovascular disease; liver diseases; arthritis; increased exercise capacity in older subjects; HIV infection; viral replication; tumor reduction; erectile dysfunction: **inflammatory** bowel disease, and ulcerative colitis. Additional indications treatable using this invention include, but are not limited to, **inflammatory**, degenerative articular and extra-articular rheumatic disorders, non-rheumatic states of **inflammation** and swelling, arthrosis deformans, chondropathies, periarthritis, neurodermitis and psoriasis, alcoholic, hepatic and uraemic origin, degeneration of the liver parenchyma, hepatitis, fatty liver and fatty cirrhosis as well as chronic liver disorders, bronchial **asthma**, sarcoidosis, and ARDS (acute **respiratory** distress syndrome).

L4 ANSWER 4 OF 7 USPATFULL

AB The present invention describes methods for synthesizing novel dithiolane derivatives, ligands with high affinity for the nuclear hormone receptors, peroxisome proliferator-activated receptor-.gamma. (PPAR.gamma.) and/or PPAR.alpha.. Methods for using these compounds in the treatment of endocrine, skin, cardiovascular, immunological, neurological, neuropsychiatric, neoplastic and chronic viral diseases of various organs, including the eye are described. Methods of treating proliferative and **inflammatory** diseases, degenerative diseases, and age-related dysregulations, caused by an hereditary (genetic) condition or an environmental insult are also provided. In addition, methods are provided for treating conditions and diseases comprising the step of administering to a human or an animal in need thereof a therapeutic amount of pharmacological compositions comprising a pharmaceutically acceptable carrier, a PPAR.alpha. agonist, and a second agent selected from the following: a PPAR.gamma. ligand, or an RXR ligand (rexinoid), or a PPAR.gamma./RXR ligand, effective to reverse, slow, stop, or prevent the pathological **inflammatory** or degenerative process.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 2002:75470 USPATFULL |
| TITLE: | Dithiolane derivatives |
| INVENTOR(S): | Pershadsingh, Harrihar A., Bakersfield, CA, United States<br>Avery, Mitchell A., Oxford, MS, United States |
| PATENT ASSIGNEE(S): | Bethesda Pharmaceuticals, Inc., Bakersfield, CA, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 6369098 | B1 | 20020409 | |
| APPLICATION INFO.: | US 2000-684738 | | 20001004 | (9) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1999-157890P | 19991005 | (60) |
| | US 2000-185347P | 20000226 | (60) |
| | US 2000-225907P | 20000817 | (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | GRANTED |
| PRIMARY EXAMINER: | Lambkin, Deborah C. |
| LEGAL REPRESENTATIVE: | Townsend and Townsend and Crew LLP |

NUMBER OF CLAIMS: 42
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 22 Drawing Figure(s); 22 Drawing Page(s)
LINE COUNT: 3404
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . neurological, neuropsychiatric, neoplastic and chronic viral diseases of various organs, including the eye are described. Methods of treating proliferative and **inflammatory** diseases, degenerative diseases, and age-related dysregulations, caused by an hereditary (genetic) condition or an environmental insult are also provided. In. . . PPAR.gamma. ligand, or an RXR ligand (rexinoid), or a PPAR.gamma./RXR ligand, effective to reverse, slow, stop, or prevent the pathological **inflammatory** or degenerative process.

SUMM . . . a role in other processes. Binding of ligands to PPARs induce changes in the transcriptional activity of genes that modulate **inflammatory** processes, angiogenesis, cellular proliferation and differentiation, apoptosis, and the activities of iNOS, MMPases and TIMPs. These findings suggest that regulation. . . have a therapeutic role in treating diseases such as occlusive vascular diseases (e.g. atherosclerosis), hypertension, neovascular diseases (e.g. diabetic retinopathy), **inflammatory** diseases (e.g. **inflammatory** bowel disease and psoriasis), and neoplastic diseases (carcinogenesis).

SUMM . . . processes relevant to disease. For example, PPAR.alpha. or PPAR.gamma. may either have similar or disparate effects. It is known that **inflammatory** activation of human aortic smooth-muscle cells is inhibited by PPAR.alpha., but not by PPAR.gamma.. Apoptosis in human monocyte-derived macrophages is. . .

SUMM The present invention provides novel dithiolane derivatives which can be used to ameliorate PPAR.gamma.-mediated diseases such as **inflammatory** and proliferative diseases and those that are characterized by inappropriate activation of nuclear transcription factors.

DETD The term "**inflammatory** disease" includes diseases (treatable or preventable with compounds described in this invention) including, but not limited to,

DETD b. **inflammatory** cytokine (e.g. TNF-alpha, interleukin (IL)-1-alpha, IL-1-beta, IL-2, IL-6) production

DETD c. activation of nuclear factors that promote transcription of genes encoding **inflammatory** cytokines. Examples of these nuclear transcription factors include but are not restricted to: nuclear factor-kappaB (NF-kappaB), activated protein-1 (AP-1), nuclear. . .

DETD . . . used to treat diseases involving tissues that express PPAR.gamma., PPAR.alpha. and PPAR.delta., and more particularly, can be used for treating **inflammatory**, proliferative, degenerative diseases of multiple organs and tissues, and diseases involving pathological angiogenesis and neovascularization. Advantageously, the compounds can be. . .

DETD . . . "modify and modulate" are defined to include its usually accepted meaning and includes treating a human subject prophylactically to alter **inflammation**, apoptosis, proliferation, angiogenesis, neovascularization, immune dysfunction, and expression of oncogenes and other genes controlling cell metabolism. The present method includes. . .

DETD . . . of dermatological diseases (Table I), psychiatric disorders (Table II), neurodegenerative diseases (Table III), diseases associated with allograft transplantation (Table IV), **inflammatory** or degenerative diseases in multiple organ systems (Table V), neoplastic diseases (Table VIa, Table VIb), diseases caused by naked or coated DNA

and RNA viruses (Table VII), diseases associated with human immunodeficiency virus (HIV) infection (Table VIII), **inflammatory**, proliferative and degenerative diseases of the eye (Tables IXa, IXb, IXc, IXd, IXe), and clinical conditions associated with injury and. . .

DETD . . . compound and methods of the present invention are useful in treating diseases including but not limited to, a T lymphocyte-mediated **inflammatory** disease involving pathological apoptosis, a T lymphocyte-mediated disease such as allograft transplant rejection and complications thereof, an **inflammatory** disease such as a complication of allograft rejection, a T lymphocyte-mediated disease such as a neurodegenerative **inflammatory** disease, wherein neurodegenerative **inflammatory** disease is multiple sclerosis, Alzheimer's disease, or Parkinson's disease. Those of skill in the art will know of other T lymphocyte-mediated diseases and **inflammatory** diseases suitable for treatment using the present methods and compounds.

DETD . . . of the lower incidence of undesirable side effects, the compounds of this invention can be given until improvement in the **inflammatory** process or disease involving neovascularization is observed.

DETD . . . apigenin, lutein, luteolin), glutathione and its derivatives (e.g. N-acetylcysteine and dithiothreitol), and phytoestrogens and phenolic anthocyanidin and procyanidin derivatives (e.g. **resveratrol**, cyanidin, cinnamic acid).

DETD The compounds of the instant invention are further useful to suppress the mediators of neurogenic **inflammation** (e.g. substance P or the tachykinins), and may be used in the treatment of rheumatoid arthritis; psoriasis; topical **inflammation** such as is associated with sunburn, eczema, or other sources of itching; and allergies, including **asthma**. The compounds can also function as neuromodulators in the central nervous system, with useful applications in the treatment of Alzheimer's. . .

DETD . . . and PPAR.alpha. activators. Activation of both PPAR.gamma. and PPAR.alpha. have effects on metabolic risk factors that lead to chronic systemic **inflammation** that can result in diabetes, atherosclerosis, congestive heart failure, ulcerative colitis, rheumatoid arthritis, osteoporosis, Alzheimer's disease, multiple sclerosis, and other. . .

DETD . . . in the treatment of atherosclerosis or psoriasis, respectively dermatological and vascular (arterial) manifestations of a diseases with a chronic systemic **inflammatory** character. The pathogenesis of both atherosclerosis and psoriasis involve the inappropriate proliferation (vascular smooth muscle cells in atherosclerosis and epidermal keratinocytes in psoriasis) and expression of **inflammatory** cytokines, mediated by activation of the **inflammatory** transcription factors, NF-kappaB, AP-1 and NFAT (see, Neve et al. Biochem Pharmacol, 60:1245-1250 (2000) and Ellis et al. Arch Dermatol,136:609-16. . .

DETD Via negative regulation of NF-kappaB and AP-1 signaling pathways, PPAR.alpha. inhibits expression of **inflammatory** genes, such as interleukin-6, cyclooxygenase-2, endothelin-1, and the expression of monocyte-recruiting proteins such as vascular cell adhesion molecule (VCAM)-1, and. . . of PPAR.gamma. and PPAR.alpha. provides a synergistic therapeutic effect and leads to superior improvement, resolution or prevention of systemic cardiovascular **inflammation** , including atherosclerosis, vascular restenosis, congestive heart failure and myocardial fibrosis (see, Takano H, et al. Circ Res,

87:596-602 (2000); Lee. . .

DETD In certain instances, both PPAR.gamma. and PPAR.alpha. activators have been shown, independently, to suppress expression of **inflammatory** regulators, inhibit proliferation and promote apoptosis of pathological cellular phenotypes. Paradoxically and unexpectedly, the opposite case occurs wherein the therapeutic. . . of apoptosis is the operative mechanism. Therefore, in these disease states, activation of PPAR.gamma. and PPAR.alpha. by suppressing transcription of **inflammatory** cytokines, prevents apoptosis of the target cell and promotes survival of the non-pathological cellular phenotype. For example, in the case. . . amnestic T lymphocytes lacking immune recognition of oligodendrocytes, and inappropriately activated microglia, resulting in inappropriately activation and production of harmful **inflammatory** cytokines (see, Zhang, GX et al. Mult Scler, 6:3-13 (2000)). PPAR.gamma. activation can inhibit neuronal apoptosis and promote neuronal protection. . . cells from cytokine-induced apoptotic cell death (Heneka, MT et al. J Neuroimmunol.,100:156-68 (1999)). Moreover, PPAR.alpha. has been shown to suppress **inflammatory** cytokines and nuclear factors in monocyte/macrophages. A similar mechanism involving suppression of **inflammatory** cytokine production by microglia would prevent oligodendrocyte apoptosis. Finally, combined PPAR.gamma. and PPAR.alpha. activation promotes Th1/Th2 differentiation as a final. . .

DETD . . . the disease or improvement in his clinical status is evaluated by monitoring improvement in motor deficits. Reduction of the systemic **inflammation** associated with the disease is assessed by performing bimonthly measurements of high sensitivity-C-reactive protein (hs-CRP). A reduction in the hs-CRP. . .

DETD Combination Treatment of a PPAR-Mediated **Inflammatory**, Proliferative or Degenrative Disease with PPARalpha Agonist and a PPARgamma Agonist--A Clinical Trial

DETD . . . diabetes mellitus, cardiomyopathy, congestive heart failure, myocardial ischemia, organ fibrosis (hepatic, pulmonary or myocardial), thrombosis, a carcinogenic disease, or other **inflammatory**, proliferative, or degenerative disease (Horrocks LA and Yeo YK, Pharmacol Res, 40:211-25 (1999); Youdim, KA, Int J Dev Neurosci., 18:383-99. . .

DETD . . . acutely or chronically with the manifestations of Alzheimer's disease (a neuro-degenerative disease), glaucomatous retinopathy (a neuro-retinal degenerative disease), atherosclerosis (an **inflammatory** ischemic vascular disease), ulcerative colitis (an **inflammatory** bowel disease), hepatic fibrosis (a degenerative liver disease), or breast or prostate cancer (a carcinogenic disease). The diagnosis is confirmed. . . maintenance dose of 30 mg. The patient's response to therapy is monitored by laboratory markers of the respective disease, and **inflammatory** markers of systemic **inflammation** to monitor amelioration of the **inflammatory** response to assess clinical improvement.

DETD Treatment of a PPAR-Mediated **Inflammatory**, Proliferative or Degenerative Disease with Compound which Activates both PPARalpha and PPARgamma--A Clinical Trial

DETD . . . i.e. is a co-ligand for PPARgamma and PPARalpha, is the active ingredient of the pharmacological composition used to treat the **inflammatory**, proliferative or degenerative disease. Examples of such compounds are the 3-substituted benzodithiolanyl derivatives described in this invention (typical doses are. . .

DETD Combination Treatment of a PPAR-Mediated **Inflammatory**, Proliferative or Degenerative Disease with PPARgamma Agonist or a Mixed

PPARgamma/PPARalpha Agonist (Co-Ligand) and an Estrogen Receptor Ligand--A Clinical Trial

DETD . . . disease, arthritis, atherosclerosis, depression, diabetes mellitus, cardiomyopathy, congestive heart failure, myocardial infarction, organ fibrosis, thrombosis, a carcinogenic disease, or other **inflammatory**, proliferative, or degenerative disease (Horrocks, LA and Yeo, YK, Pharmacol Res., 40:211-25 (1999); Youdim, KA, Int J Dev Neurosci., 18:383-99. . .

DETD . . . or chronically with the manifestations of Alzheimer's disease (a neuro-degenerative disease), glaucomatous retinopathy (a neuro-retinal degenerative disease), atherosclerosis (an **inflammatory** ischemic vascular disease), ulcerative colitis (an **inflammatory** bowel disease), hepatic fibrosis (a degenerative liver disease), or a carcinogenic disease of the breast or prostate. The diagnosis is. . . treatment and monthly thereafter. The patient's response to therapy is additionally monitored by laboratory markers of the respective disease, and **inflammatory** markers of systemic **inflammation** to monitor amelioration of the **inflammatory** response to determine clinical improvement.

DETD Combination Treatment of a PPAR-Mediated **Inflammatory**, Proliferative Dermatological (Skin) Disease with PPARgamma Agonist or a Mixed PPARaamma/PPARalpha Agonist (Co-Ligand) and a Vitamin D Receptor Ligand--A Clinical. . .

DETD The PPAR-mediated disease is an **inflammatory**, proliferative or degenerative skin disease such as psoriasis, keratitis, hidradenitis, ichthyosis, acne, rosacea, verrucae and other HPV infections, atopic dermatitis,. . .

DETD . . . common warts, anogenital (venereal) warts, viral warts including human papilloma virus (HPV) infections, conjunctival warts, oral/buccal warts)

Acute and chronic dermatitides (**inflammation** of the skin), atopic derma-
titis, allergic dermatitis, contact dermatitis, cosmetic dermatitis, chemical dermatitis, seborrheic dermatitis, solar dermatitis, acute and
. . .

DETD

TABLE IV

Examples of **inflammatory** and metabolic disorders associated with allograft transplantation treatable using compounds described in this invention

The compounds described herein are useful as monotherapy or adjunctive therapy with existing immunosuppressive agents for the promotion and maintenance of allograft survival, post-transplantation.

Examples of **inflammatory** and proliferative conditions or diseases associated with allograft transplantation and immune suppression include:

1. Acute allograft rejection
2. Chronic allograft rejection
3. Graft versus. . .

DETD . . . endometritis, endometriosis, benign prostatic hypertrophy, leiomyoma, polycystic kidney disease (e.g. autosomal dominant PKD), acute tubular necrosis, nephrotic syndrome, diabetic nephropathy, glomerulonephritis

**Pulmonary Asthma, chronic obstructive pulmonary disease (COPD)**, reactive airway disease, pulmonary fibrosis, pulmonary hypertension.

Connective tissue
Joint Rheumatoid arthritis, Raynaud's phenomenon/disease, Sjogren's syndrome, systemic sclerosis, systemic lupus erythematosus, **inflammatory** bowel disease (ulcerative colitis, Crohn's disease) vasculitides, ankylosing spondylitis, osteoarthritis, reactive arthritis, psoriatic arthritis, fibromyalgia, osteoarthritis, sarcoidosis.
Liver/Other Hepatic fibrosis, hepatic. . .
DETD . . . diseases of the eye.
HAV, Hepatitis, hepatocellular carcinoma, lymphoma.
HBV,
HCV
CMV Hepatitis, retinitis, meningitis.
HSV, Related mucocutaneous, oropharyngeal and genital diseases,
VSV related skin and **respiratory** infections, varicella-zoster, chicken pox, herpes zoster, post-herpetic neuralgia, conjunctivitis, keratoconjunctivitis, keratitis.
HHV Exanthem subitum, infectious mononucleosis.
EBV Infectious mononucleosis, chronic fatigue syndrome, lymphoma, conjunctivitis, keratitis, and related infections of the eye.
Adeno- Upper and lower **respiratory** tract infections, pneumonia,
viruses conjunctivitis.
RSV Upper and lower **respiratory** tract infections, pneumonia.
PMV Mumps and related manifestations, e.g., conjunctivitis.
MV, RV Measles, Rubella ("German measles") and related manifestations.
Coxsackie Conjunctivitis, diabetes mellitus, **respiratory** infections.
viruses
Influenza Upper and lower **respiratory** tract infections, pneumonia.
viruses

HIV, Human Immunodeficiency Virus; HTLV, Human T-cell Lymphocyte Virus; HPV, Human Papilloma Virus; HAV, Hepatitis A Virus; HBV,. . . C Virus; CMV, Cytomegalovirus; HSV, Herpes Simplex Virus (Types I & II); HHV, Human Herpes Virus; EBV, Epstein-Barr Virus; RSV, **Respiratory** Syncytial Virus; VZV, Varicella-Zoster Virus; PMV, Paramyxovirus; MV, Measles (Rubeola) Virus; RV, Rubella Virus
DETD
TABLE IXa

Diseases of the eye treatable using compounds described in this invention
1. **Inflammatory** eye diseases associated with viral infections
Disease Virus

Blepharitis HSV, VZV, Vaccinia, HPV, molluscum contagiosum
Conjunctivitis HSV, VZV, BBV, Adenovirus, Vaccinia, Variola, HPV,
. . .
DETD . . . diseases treatable using compounds described in this invention (cont'd)
Disease Category/Examples of Diseases, Causes or Associated Conditions

Conjunctivitis Acute allergic conjunctivitis (e.g. drug-related **inflammation**, hypersensitivity reactions), chronic (vernal) conjunctivitis, contact lens-associated conjunctivitis, e.g. giant papillary conjunctivitis, conjunctival ulceration,

including ulceration associated with mucous membrane, conjunctival warts
Blepharitis **Inflammatory** etiologies, e.g. blepharitis secondary to rosacea
Ophthalmic fibrosis Steven's-Johnson syndrome with progressive fibrosis and scarring, cicatrization and symblepharon.
Corneal injury Corneal abrasion. . .
CLM What is claimed is:
36. A method for treating an **inflammatory** and or degenerative disease of mammalian tissues, said method comprising: administering to a mammal in need thereof a therapeutic amount. . . ligand, a PPAR.gamma./RXR ligand and Vitamin D or an analog thereof effective to reverse, slow, stop, or prevent the pathological **inflammatory** and or degenerative process.

42. The method in accordance with claim 36, wherein said disease is an **inflammatory** or degenerative skin disease and includes psoriasis, keratitis, hidradenitis, ichthyosis, acne, rosacea, verrucae and other HPV infections, atopic dermatitis, allergic. . .

L4 ANSWER 5 OF 7 USPATFULL
AB This invention relates to compositions derived from Chinese herbal medicines, medicinal plants and extracts thereof, and to their use for the treatment of animals infected with viruses, especially with hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). More specifically, the compositions of the present invention arc derived from various Chinese herbal medicines or medicinal plants which have a long history of human consumption. The compositions of the invention are obtained through specific techniques and have demonstrated outstanding efficacy for treating human HBV carriers and hepatitis C patients. Compositions according to the invention have also exhibited in vitro antiviral activities against murine leukemia virus (MuLV) and HIV. HIV is the virus known to cause acquired immunodeficiency syndrome (AIDS) in humans and AIDS presents special problems to the medical community which the present invention addresses.

| | |
|---|---|
| ACCESSION NUMBER: | 2001:51574 USPATFULL |
| TITLE: | Process for preparing an anti-viral medicinal product from plant extracts |
| INVENTOR(S): | Hwang, Shie-Ming, 4886 Chevy Chase Ave., Columbus, OH, United States 43220 |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6214350 | B1 | 20010410 |
| APPLICATION INFO.: | US 1999-376701 | | 19990817 (9) |
| RELATED APPLN. INFO.: | Division of Ser. No. US 1997-890065, filed on 9 Jul 1997, now patented, Pat. No. US 5989556 | | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1996-16100P | 19960710 (60) |

| | |
|---|---|
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Tate, Christopher R. |
| LEGAL REPRESENTATIVE: | Standley & Gilcrest LLP |

NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 34 Drawing Figure(s); 29 Drawing Page(s)
LINE COUNT: 3439

SUMM Hepatitis is a disease of the human liver. It is manifested with **inflammation** of the liver and is usually caused by viral infections and sometimes from toxic agents. Hepatitis may progress to liver. . .

SUMM . . . medicines known as LESPEDEZAE HERBA and SENECINIS HERBA have traditionally been used to treat illnesses such as urine incontinence, gonorrhea, **asthma**, stomach ache, general weakening and exhaustion, diarrhea, contusion injury, eye disease, eye redness, renal disease, acute **inflammatory** disease, cataract, dysentery, enteritis, jaundice, flu, septicemia, sore, swelling, and a disease of the palm. LESPEDEZAE HERBA is prepared from. . .

SUMM . . . japonicum which belongs to the family Oleaceae. The leaves of Ligustrum lucidum have been used as an antipyretic, analgesic, and anti-**inflammatory** agent. The leaves of Ligustrum japonicum have also been used to treat illnesses such as ophthalmalgia, ulcerative stomatitis, mastitis, swelling,. . .

SUMM . . . Lonicera japonica or Lonicera confusa. Both plants belong to the family Caprifoliaceae. The flower of Lonicera japonica has diuretic, antipyretic, anti-**inflammatory**, anti-convulsive, antibacterial and antiviral properties. The flower bud has also been used as a diuretic. The herbal medicine tastes sweet. . .

SUMM . . . crude flavenoids from Scutellaria baicalensis has been shown to have antibacterial and antiviral properties. A group of patients with severe **respiratory** disease were treated with the mixture and they responded as well as a control group on standard antibiotic therapy. See. . .

SUMM . . . also been used to prepare an eye wash, for strengthening stomach and intestine to stimulate appetite, and as an astringent, anti-**inflammatory**, etc. It has antibacterial, anti-**inflammatory**, and wound healing properties. PHELLODENDRI CORTEX is prepared from the dried cortex of plants from the Rutaceae family such as. . .

SUMM **Resveratrol** has been reported as an antifungal and antibacterial component in the root of Polygonum cuspidatum, See H. Y. Hsu, Y.. . .

SUMM . . . been used to treat illnesses such as hematemesis, gonorrhea with traces of blood, sores, cancer, convulsion, pneumonia, enteritis, coccygodynia, appendicitis, **asthma**, malaria, and rheumatism. It was also found to have antibacterial effect. SCUTELLARIAE BARBATAE HERBA is prepared from the dried whole. . .

SUMM . . . the dried whole plant of Solanum nigrum which belongs to the family Solanaceae. The extract of SOLANI HERBA has demonstrated anti-**inflammatory** property. The fruit has also exhibited the effects of suppressing coughs and relieving bronchial **inflammation**. The herbal medicine tastes bitter and slightly sweet, and is nontoxic. Treatment dosage is typically 11 to 60 g per. . .

SUMM The compound solasonine (found in the whole herb, fruit, leaf, and fresh immature berries of Solanum nigrum) has an anti-**inflammatory** effect similar to cortisone. Solasonine and solanine (also found in Solanum nigrum) possess the ability of raising or lowering the. . .

L4 ANSWER 6 OF 7 USPATFULL

AB Compositions derived from Chinese herbal medicines, medicinal plants and extracts thereof, are provided for the treatment of animals infected

with viruses, especially with hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). More specifically, the compositions of the present invention are derived from various Chinese herbal medicines or medicinal plants which have a long history of human consumption. The compositions of the invention are obtained through specific techniques and have demonstrated outstanding efficacy for treating human HBV carriers and hepatitis C patients. Compositions according to the invention have also exhibited in vitro antiviral activities against murine leukemia virus (MuLV) and HIV. HIV is the virus known to cause acquired immunodeficiency syndrome (AIDS) in humans and AIDS presents special problems to the medical community which the present invention addresses. Preferred compositions contain the herbal ingredients AEGINETIAE HERBA, BLECHNI RHIZOMA, LESPEDEZAE HERBA, POLYGONI CUSPIDATI RHIZOMA, FORSYTHIAE FRUCTUS, and LIGUSTRI FRUCTUS, or contain the herbal ingredients AEGINETIAE HERBA, LONICERAE FLOS, PRUNELLAE SPICA, and LESPEDEZAE HERBA.

ACCESSION NUMBER: 1999:150659 USPATFULL
TITLE: Compositions of matter useful in the treatment of viral infections derived from plant extracts
INVENTOR(S): Tsai, Hsiu-Hsien, Chang-Huah, Taiwan, Province of China
Hwang, Shie-Ming, Columbus, OH, United States
PATENT ASSIGNEE(S): Sage R&D, Columbus, OH, United States (U.S. corporation)

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5989556 | | 19991123 | |
| APPLICATION INFO.: | US 1997-890065 | | 19970709 | (8) |

| | NUMBER | DATE | |
|---|---|---|---|
| PRIORITY INFORMATION: | US 1996-16100P | 19960710 | (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Naff, David M.
ASSISTANT EXAMINER: Kerr, Janet M.
LEGAL REPRESENTATIVE: Nickey, Donald O.Standley & Gilcrest, LLP
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
LINE COUNT: 3305

SUMM Hepatitis is a disease of the human liver. It is manifested with **inflammation** of the liver and is usually caused by viral infections and sometimes from toxic agents. Hepatitis may progress to liver. . .

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SUMM . . . japonicum which belongs to the family Oleaceae. The leaves of Ligustrum lucidum have been used as an antipyretic, analgesic, and anti-**inflammatory** agent. The leaves of Ligustrum japonicum have also been used to treat illnesses such as ophthalmalgia, ulcerative stomatitis, mastitis, swelling,. . .

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the family Caprifoliaceae. The flower of Lonicera japonica has diuretic, antipyretic, anti-**inflammatory**, anti-convulsive, antibacterial and antiviral properties. The flower bud has also been used as a diuretic. The herbal medicine tastes sweet. . .

SUMM . . . crude flavonoids from Scutellaria baicalensis has been shown to have antibacterial and antiviral properties. A group of patients with severe **respiratory** disease were treated with the mixture and they responded as well as a control group on standard antibiotic therapy. See. . .

SUMM . . . also been used to prepare an eye wash, for strengthening stomach and intestine to stimulate appetite, and as an astringent, anti-**inflammatory**, etc. It has antibacterial, anti-**inflammatory**, and wound healing properties. PHELLODENDRI CORTEX is prepared from the dried cortex of plants from the Rutaceae family such as. . .

SUMM **Resveratrol** has been reported as an antifungal and antibacterial component in the root of Polygonum cuspidatum. See H. Y. Hsu, Y.. . .

SUMM . . . been used to treat illnesses such as hematemesis, gonorrhea with traces of blood, sores, cancer, convulsion, pneumonia, enteritis, coccygodynia, appendicitis, **asthma**, malaria, and rheumatism. It was also found to have antibacterial effect. SCUTELLARIAE BARBATAE HERBA is prepared from the dried whole. . .

SUMM . . . the dried whole plant of Solanum nigrum which belongs to the family Solanaceae. The extract of SOLANI HERBA has demonstrated anti-**inflammatory** property. The fruit has also exhibited the effects of suppressing coughs and relieving bronchial **inflammation**. The herbal medicine tastes bitter and slightly sweet, and is nontoxic. Treatment dosage is typically 11 to 60 g per. . .

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L4 ANSWER 7 OF 7 USPATFULL

AB This invention relates to compositions derived from Chinese herbal medicines, medicinal plants and extracts thereof, and to their use for the treatment of animals infected with viruses, especially with hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). More specifically, the compositions of the present invention are derived from various Chinese herbal medicines or medicinal plants which have a long history of human consumption. The compositions of the invention are obtained through specific techniques and have demonstrated outstanding efficacy for treating human HBV carriers and hepatitic C patients. Compositions according to the invention have also exhibited in vitro antiviral activities against murine leukemia virus (MuLV) and HIV. HIV is the virus known to cause acquired immunodeficiency syndrome (AIDS) in humans and AIDS presents special problems to the medical community which the present invention addresses.

| | |
|---|---|
| ACCESSION NUMBER: | 1998:143667 USPATFULL |
| TITLE: | Use of plant extracts for treatment of HIV, HCV and HBV infections |
| INVENTOR(S): | Tsai, Hsiu-Hsien, Chang-Huah, Taiwan, Province of China<br>Hwang, Shie-Ming, Columbus, OH, United States<br>Kung, Pai-Chu, Chaug-Huah, Taiwan, Province of China |
| PATENT ASSIGNEE(S): | Sage R&D, Columbus, OH, United States (U.S. |

corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 5837257 | | 19981117 |
| APPLICATION INFO.: | US 1997-863803 | | 19970527 (8) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1996-16100P | 19960710 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Naff, David M.
ASSISTANT EXAMINER: Kerr, Janet M.
LEGAL REPRESENTATIVE: Nickey, Donald O.Standley & Gilcrest
NUMBER OF CLAIMS: 13
EXEMPLARY CLAIM: 1
LINE COUNT: 2073

SUMM Hepatitis is a disease of the human liver. It is manifested with **inflammation** of the liver and is usually caused by viral infections and sometimes from toxic agents. Hepatitis may progress to liver. . .

SUMM . . . epistaxis, rashes, sores, mumps, chronic skin boils, dermatitis, anemia, fever, swollen sores, stomatitis, acute laryngitis, tonsillitis, gingivitis, parasitic oral mucosa **inflammation**, snake or dog bites, malignant sores, and erysipelas. Ethanol extracts of INDIGO PULVERATA LEVIS have exhibited bacterial inhibition properties.

SUMM . . . known as LESPEDEZAE HERBA and SENECINIS HERBA have traditionally been used to treat illnesses such as urine incontinence, gonorrhea, leucorrhoea, **asthma**, stomach ache, general weakening and exhaustion, a children's disease characterized by swelling of the belly and limbs caused by malnutrition or parasitic worms, diarrhea, contusion injuries, eye diseases, visual impairment, eye redness, renal disease, breast abscess, acute **inflammatory** disease, cataracts, dysentery, enteritis, jaundice, flu, septicemia, abscesses, boils, ringworm, erysipelas, snake or dog bites, rheumatic pains, sores, swelling and. . .

SUMM . . . japonicum which belongs to the family Oleaceae. The leaves of Ligustrum lucidum have been used as an antipyretics, analgesics and anti-**inflammatory** agents. The leaves of Ligustrum japonicum have also been used to treat illnesses such as ophthalmalgia, ulcerative stomatitis, mastitis, swelling,. . .

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SUMM . . . crude flavonoids from Scutellaria baicalensis have been shown to have antibacterial and antiviral properties. A group of patients with severe **respiratory** disease were treated with the mixture and they responded as well as a control group on standard antibiotic therapy. See. . .

SUMM . . . and Pseudomonas aeruginosa. The preparation was shown to be as effective as penicillin and aminophylline in treating bronchopneumonia and acute **bronchitis** patients. See Y. Q. Li, W. Yuan, & S. L. Zhang, Chung Kuo Chung Hsi I Chieh Ho Tsa Chih,. . .

SUMM . . . medicine has also been used as an eye wash, for strengthening stomach and intestine, stimulate appetite, and as an astringent, anti-

**inflammatory**, etc. It has antibacterial, anti-**inflammatory**, and wound healing properties. PHELLODENDRI CORTEX is prepared from the dried cortex of plants from the Rutaceae family such as. . .

SUMM **Resveratrol** has also been reported as an antifungal and antibacterial component in the root of Polygonum cuspidatum. See H. Y. Hsu,. . .

SUMM . . . or cut injuries, snake bite injuries, dysentery with traces of blood, convulsions, pneumonia, abdominal pains, congenital diseases, enteritis, coccygodynia, appendicitis, **asthma**, malaria, and rheumatism. It was also found to have antibacterial effect. SCUTELLARIAE BARBATAE HERBA is prepared from the dried whole. . .

SUMM . . . as SOLANI HERBA has traditionally been used to treat illnesses such as boils, abscesses, erysipelas, contusion or sprain injuries, chronic **bronchitis**, acute nephritis, cancer, swelling, hernia, ulcers, carbuncles with swelling and sores. SOLANI HERBA is prepared from the dried whole plant of Solanum nigrum which belongs to the family Solanaceae. Extracts of SOLANI HERBA have demonstrated anti-**inflammatory** properties. The fruit has also exhibited the effects of suppressing coughs and relieving bronchial **inflammation**. The herbal medicine tastes bitter and slightly sweet and is nontoxic. Treatment dosage is typically 11 to 60 g per. . .

SUMM The compound solasonine (found in the whole herb, fruit, leaf, and fresh immature berries of Solanum nigrum) has an anti-**inflammatory** effect similar to cortisone. Solasonine and solanine (also found in Solanum nigrum) possesses the ability of raising or lowering the. . .

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FILE 'CAPLUS' ENTERED AT 20:40:02 ON 11 JUL 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'USPATFULL' ENTERED AT 20:40:02 ON 11 JUL 2002
CA INDEXING COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)

=> s l2 and (asthma? or alveoliti? or copd or
chronic(2a)obstruct?(3a)pulmonary(2a)disease? or bronchit? or cystic(2a)fibro? or
bronchiecta? or interstitial(4a)lung)
L5          16 L2 AND (ASTHMA? OR ALVEOLITI? OR COPD OR CHRONIC(2A) OBSTRUCT?(3
               A) PULMONARY(2A) DISEASE? OR BRONCHIT? OR CYSTIC(2A) FIBRO? OR
               BRONCHIECTA? OR INTERSTITIAL(4A) LUNG)

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6           15 DUP REM L5 (1 DUPLICATE REMOVED)

=> d his

     (FILE 'HOME' ENTERED AT 20:15:59 ON 11 JUL 2002)

     FILE 'REGISTRY' ENTERED AT 20:16:18 ON 11 JUL 2002
                E RESVERATROL/CN
L1            1 S E3

     FILE 'STNGUIDE' ENTERED AT 20:17:20 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:24:43 ON 11 JUL 2002
L2         1307 S (L1 OR RESVERATROL?)
L3            7 S L2 AND RESPIRAT? AND INFLAMMAT? AND (ASTHMA? OR ALVEOLITI? OR
L4            7 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 20:36:40 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:40:02 ON 11 JUL 2002
L5           16 S L2 AND (ASTHMA? OR ALVEOLITI? OR COPD OR CHRONIC(2A)OBSTRUCT?
L6           15 DUP REM L5 (1 DUPLICATE REMOVED)

=> s l6 not l3
L7            8 L6 NOT L3

=> d l7 abs ibib kwic 1-8

L7   ANSWER 1 OF 8  CAPLUS  COPYRIGHT 2002 ACS
AB   Compns. and methods for therapy of cystic fibrosis and
     other conditions are provided.  The compns. comprise one or more compds.
     such as flavones and/or isoflavones capable of stimulating chloride
     transport in epithelial tissues.  Therapeutic methods involve the
     administration (e.g., orally or via inhalation) of such compns. to a
     patient afflicted with cystic fibrosis and/or another
     condition responsive to stimulation of chloride transport.
ACCESSION NUMBER:        2001:895652  CAPLUS
DOCUMENT NUMBER:         136:31706
TITLE:                   Compositions and methods for cystic
                         fibrosis therapy
```

09/694,108

INVENTOR(S): Fischer, Horst; Illek, Beate
PATENT ASSIGNEE(S): Children's Hospital Oakland Research Institute, USA
SOURCE: U.S., 50 pp., Cont.-in-part of U.S. 5,972,995.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6329422 | B1 | 20011211 | US 1998-174077 | 19981016 |
| US 5972995 | A | 19991026 | US 1997-951912 | 19971016 |

PRIORITY APPLN. INFO.: US 1997-951912 A2 19971016
OTHER SOURCE(S): MARPAT 136:31706
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Compositions and methods for **cystic fibrosis** therapy

AB Compns. and methods for therapy of **cystic fibrosis** and other conditions are provided. The compns. comprise one or more compds. such as flavones and/or isoflavones capable of stimulating chloride transport in epithelial tissues. Therapeutic methods involve the administration (e.g., orally or via inhalation) of such compns. to a patient afflicted with **cystic fibrosis** and/or another condition responsive to stimulation of chloride transport.

ST **cystic fibrosis** treatment flavone isoflavone chloride transport

IT Cell membrane
(CFTR trafficking to; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Chaperonins
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(analogs; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Drug delivery systems
(carriers; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Epithelium
(chloride transport in; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Sweat gland
(duct; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Intestine
Mammary gland
Respiratory tract
(epithelium; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT **Cystic fibrosis**
Gallbladder
Mammalia
Pancreas
Salivary gland
(flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)

IT Chloride channel
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(flavone and isoflavone compns. and methods for **cystic**

**fibrosis** therapy)
IT CFTR (**cystic fibrosis** transmembrane conductance regulator)
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Flavones
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Drug delivery systems
(inhalants; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Biological transport
(of chloride; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Drug delivery systems
(oral; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Mutation
(point; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT Phenols, biological studies
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyphenols, nonpolymeric; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT 380681-30-1 380681-31-2
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(amino acid sequence; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT 56-81-5, Glycerol, biological studies 67-68-5, Dimethylsulfoxide, biological studies 74-89-5, Methylamine, biological studies 1184-78-7, Trimethylamine N-oxide 23522-05-6, Taurin 89149-10-0, Deoxyspergualin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as chaperone; flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT 446-72-0, Genistein
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT 50-81-7, Ascorbic acid, biological studies 50-81-7D, Ascorbic acid, salts 117-39-5, Quercetin 153-18-4, Rutin 156-54-7, Sodium butyrate 486-66-8, Daidzein 487-26-3, Flavanone 490-83-5, Dehydroascorbic acid **501-36-0**, **Resveratrol** 528-48-3, Fisetin 552-59-0, Prunetin 1821-12-1, Benzenebutanoic acid 17306-46-6, Apigenin 7-O-neohesperidoside
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavone and isoflavone compns. and methods for **cystic fibrosis** therapy)
IT 16887-00-6, Chloride, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(transport of; flavone and isoflavone compns. and methods for

**cystic fibrosis** therapy)

IT 380696-61-7, 1: PN: US6329422 SEQID: 1 unclaimed DNA 380696-63-9, 3: PN: US6329422 SEQID: 3 unclaimed DNA 380696-64-0, 5: PN: US6329422 SEQID: 5 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; compns. and methods for **cystic fibrosis** therapy)

IT 380696-62-8
RL: PRP (Properties)
(unclaimed protein sequence; compns. and methods for **cystic fibrosis** therapy)

L7 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB A series of **resveratrol** derivs. showing leukotriene D4 antagonism was tested as a possible potent drug for anti-**asthmatic** therapy. The synthetic method of 13 candidates was shown. Male Hartley guinea pigs weighing 400-500 g were used to test the biol. activities of the compds. The **resveratrol** derivs. used for the quant. structure-activity relationships (QSARs) calcn. in the authors' previous paper showed an av. EC50 of 604 mg/mL, while the compds. studied in this work showed 9.77 mg/mL. The structural difference between the **resveratrol** derivs. used for the QSARs calcn. and those of this work is the presence of the hydrolysis of methoxy group, because LTD4 has several hydroxyl group. Thus, to improve LTD4 antagonism of **resveratrol** derivs., they should have hydroxyl groups instead of methoxy groups.

ACCESSION NUMBER: 2001:336245 CAPLUS
DOCUMENT NUMBER: 135:235883
TITLE: **Resveratrol** derivatives showing the leukotriene D4 antagonism
AUTHOR(S): Koh, Dongsoo; Park, Kwan Ha; Lee, Heseung; Jung, Jihyun; Lim, Yoongho
CORPORATE SOURCE: Department of Applied Biology & Chemistry, Konkuk University, Seoul, 143-701, S. Korea
SOURCE: Agricultural Chemistry and Biotechnology (English Edition) (2001), 44(1), 32-34
CODEN: ACBTFF; ISSN: 1229-2737
PUBLISHER: Korean Society of Agricultural Chemistry and Biotechnology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Resveratrol** derivatives showing the leukotriene D4 antagonism

AB A series of **resveratrol** derivs. showing leukotriene D4 antagonism was tested as a possible potent drug for anti-**asthmatic** therapy. The synthetic method of 13 candidates was shown. Male Hartley guinea pigs weighing 400-500 g were used to test the biol. activities of the compds. The **resveratrol** derivs. used for the quant. structure-activity relationships (QSARs) calcn. in the authors' previous paper showed an av. EC50 of 604 mg/mL, while the compds. studied in this work showed 9.77 mg/mL. The structural difference between the **resveratrol** derivs. used for the QSARs calcn. and those of this work is the presence of the hydrolysis of methoxy group, because LTD4 has several hydroxyl group. Thus, to improve LTD4 antagonism of **resveratrol** derivs., they should have hydroxyl groups instead of methoxy groups.

ST **resveratrol** deriv prepn structure leukotriene D4 **asthma**

; hydrophilicity hydroxyl methoxy group structure **resveratrol** deriv **asthma**

IT Structure-activity relationship
(**asthma**-inhibiting; **resveratrol** derivs. prepn. and structure-related leukotriene D4 antagonism)

IT Structure-activity relationship
(leukotriene-inhibiting; **resveratrol** derivs. prepn. and structure-related leukotriene D4 antagonism)

IT Antiasthmatics
Hydrophilicity
Hydroxyl group
Methoxy group
Stereochemistry
(**resveratrol** derivs. prepn. and structure-related leukotriene D4 antagonism)

IT **501-36-0DP**, **Resveratrol**, derivs. **501-36-0P**
15058-36-3P 17861-18-6P 18221-50-6P 19826-55-2P 34708-54-8P
63877-76-9P 110983-43-2P 143207-60-7P 150258-84-7P 150809-44-2P
354761-93-6P 354761-94-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**resveratrol** derivs. prepn. and structure-related leukotriene D4 antagonism)

IT 73836-78-9, leukotriene D4
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**resveratrol** derivs. prepn. and structure-related leukotriene D4 antagonism)

L7 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB Through a series of in vitro anal. with passive cutaneous anaphylaxis on MeOH, methylene chloride, and ethylacetate exts. from 50 higher plants, effective substances were identified. The activities of these exts. were confirmed through the leukotriene D4 (LTD4) antagonism in guinea pig ileum. After the sepn. of active exts., the structures of the single compds. were detd. As a lead compd., **resveratrol**, one of the stilbene derivs. isolated from Morus alba was selected. Because of its known structure and low activity, several classes of analogs were synthesized to improve its activity with the aid of quant. structure-activity relationship (QSAR) calcns. The first training set used for QSAR calcns. was composed of 20 stilbene derivs. Based on the above QSAR calcns., relationships between structural parameters of stilbene derivs. and LTD4 antagonism were established. From the relationships, 13 candidates were predicted and synthesized. The av. of LTD4 antagonisms of those compds. was EC50 of 17.68 .mu.g/mL. These 13 compds. used for the second training set included an ethenyl group. Even though 4-benzyloxyphenol used for the first training set did not include an ethenyl group, it showed the best activity of 0.1 .mu.g/mL among the compds. tested. Therefore, by modifying the ethenyl group of the second training set into methylene oxide similar to 4-benzyloxyphenol, 4-benzyloxyphenyl butyrate, named DK-II-22, was put up as a candidate. While its predicted activity was 0.71 .mu.g/mL (EC50), the exptl. value was 1.60 .mu.g/mL (EC50). Although there is a small difference between the exptl. value and the calcd. value, the activity was improved tenfold compared to that of the second training set. A study was conducted to investigate the substitution of the ethenyl group with methylene oxide which resulted in an increment in the activity. Results indicated that

the stilbene derivs. with methylene oxide were found to be valuable and should be synthesized in future works.

ACCESSION NUMBER: 2001:148880 CAPLUS
DOCUMENT NUMBER: 135:174645
TITLE: Relationships between electron densities of stilbene moieties and leukotriene D4 antagonism
AUTHOR(S): Koh, Dongsoo; Park, Kwan Ha; Lee, Heseung; Jung, Jihyun; Kim, Kyeongmi; Cho, Somi Kim; Lim, Yoongho
CORPORATE SOURCE: Department of Applied Chemistry, Dongduk Women's University, Seoul, 136-714, S. Korea
SOURCE: Agricultural Chemistry and Biotechnology (English Edition) (2000), 43(4), 281-284
CODEN: ACBTFF; ISSN: 1229-2737
PUBLISHER: Korean Society of Agricultural Chemistry and Biotechnology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Through a series of in vitro anal. with passive cutaneous anaphylaxis on MeOH, methylene chloride, and ethylacetate exts. from 50 higher plants, effective substances were identified. The activities of these exts. were confirmed through the leukotriene D4 (LTD4) antagonism in guinea pig ileum. After the sepn. of active exts., the structures of the single compds. were detd. As a lead compd., **resveratrol**, one of the stilbene derivs. isolated from Morus alba was selected. Because of its known structure and low activity, several classes of analogs were synthesized to improve its activity with the aid of quant. structure-activity relationship (QSAR) calcns. The first training set used for QSAR calcns. was composed of 20 stilbene derivs. Based on the above QSAR calcns., relationships between structural parameters of stilbene derivs. and LTD4 antagonism were established. From the relationships, 13 candidates were predicted and synthesized. The av. of LTD4 antagonisms of those compds. was EC50 of 17.68 .mu.g/mL. These 13 compds. used for the second training set included an ethenyl group. Even though 4-benzyloxyphenol used for the first training set did not include an ethenyl group, it showed the best activity of 0.1 .mu.g/mL among the compds. tested. Therefore, by modifying the ethenyl group of the second training set into methylene oxide similar to 4-benzyloxyphenol, 4-benzyloxyphenyl butyrate, named DK-II-22, was put up as a candidate. While its predicted activity was 0.71 .mu.g/mL (EC50), the exptl. value was 1.60 .mu.g/mL (EC50). Although there is a small difference between the exptl. value and the calcd. value, the activity was improved tenfold compared to that of the second training set. A study was conducted to investigate the substitution of the ethenyl group with methylene oxide which resulted in an increment in the activity. Results indicated that the stilbene derivs. with methylene oxide were found to be valuable and should be synthesized in future works.

ST structure stilbene deriv prepn leukotriene D4 **asthma**

IT **501-36-0**, **Resveratrol**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(relationships between electron densities of stilbene moieties and leukotriene D4 antagonism)

L7 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB To develop new drugs for **asthmatic** therapy, lipid membrane derivs. have been studied. Based on the knowledge of the biosynthetic pathway, anti-**asthmatic** drugs related to the platelet-activating

factors, leukotriene and 5-lipoxygenase, are being studied. It is possible for the antagonists of leukotriene D4 (LTD4) receptor to protect smooth muscles from being contracted, and thus they could be used as anti-**asthmatic** drugs. In order to discover lead compds. as LTD4 receptor antagonists for **asthmatic** therapy, exts. of higher plants were screened. An ethylacetate ext. of a mulbery tree, Morus alba, showed an activity against bronchial contraction caused by LTD4. After more activity guided fractionation, the final active compd. was certified to be one of stilbene derivs., **resveratrol**. Recently, the rational drug design has been applied for the development of new drugs from lead compds. Studies on more stilbene derivs., however, are necessary for rational drug design. Therefore, 7 derivs., di-Me trans-stilbene-4,4'-dicarboxylate, cis-stilbene-4,4'-dicarboxylic acid, 4-amino-4'-hydroxystilbene, 4-hydroxy-4'-nitrostilbene, diethylstilbestrol, 4-benzyloxy-phenol, and chlorogenic acid, were purchased, and 13 derivs. were synthesized. Results indicated that to obtain a compd. with a high activity, the methoxy group should be hydrolyzed because the parameter related to a partition coeff. is inversely proportional to the biol. activity in the quant. structure-activity relationship equation. Moreover, the conformation between two Ph rings is independent of the activity.

ACCESSION NUMBER: 2001:148879 CAPLUS
DOCUMENT NUMBER: 135:174644
TITLE: Quantitative structure-activity relationships to develop anti-**asthmatic** drugs
AUTHOR(S): Koh, Dongsoo; Park, Kwan Ha; Lee, Heseung; Jung, Jihyun; Cho, Somi Kim; Lim, Yoongho
CORPORATE SOURCE: Department of Applied Chemistry, Dongduk Women's University, Seoul, 136-714, S. Korea
SOURCE: Agricultural Chemistry and Biotechnology (English Edition) (2000), 43(4), 277-280
CODEN: ACBTFF; ISSN: 1229-2737
PUBLISHER: Korean Society of Agricultural Chemistry and Biotechnology
DOCUMENT TYPE: Journal
LANGUAGE: English
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Quantitative structure-activity relationships to develop anti-**asthmatic** drugs

AB To develop new drugs for **asthmatic** therapy, lipid membrane derivs. have been studied. Based on the knowledge of the biosynthetic pathway, anti-**asthmatic** drugs related to the platelet-activating factors, leukotriene and 5-lipoxygenase, are being studied. It is possible for the antagonists of leukotriene D4 (LTD4) receptor to protect smooth muscles from being contracted, and thus they could be used as anti-**asthmatic** drugs. In order to discover lead compds. as LTD4 receptor antagonists for **asthmatic** therapy, exts. of higher plants were screened. An ethylacetate ext. of a mulbery tree, Morus alba, showed an activity against bronchial contraction caused by LTD4. After more activity guided fractionation, the final active compd. was certified to be one of stilbene derivs., **resveratrol**. Recently, the rational drug design has been applied for the development of new drugs from lead compds. Studies on more stilbene derivs., however, are necessary for rational drug design. Therefore, 7 derivs., di-Me trans-stilbene-4,4'-dicarboxylate, cis-stilbene-4,4'-dicarboxylic acid, 4-amino-4'-hydroxystilbene, 4-hydroxy-4'-nitrostilbene, diethylstilbestrol, 4-benzyloxy-phenol, and chlorogenic acid, were

purchased, and 13 derivs. were synthesized. Results indicated that to obtain a compd. with a high activity, the methoxy group should be hydrolyzed because the parameter related to a partition coeff. is inversely proportional to the biol. activity in the quant. structure-activity relationship equation. Moreover, the conformation between two Ph rings is independent of the activity.

IT Trachea (anatomical)
(LTD4 receptors; QSAR to develop anti-**asthmatic** drugs)

IT Antiasthmatics
Drug design
Drug screening
Mulberry (Morus alba)
(QSAR to develop anti-**asthmatic** drugs)

IT Leukotriene receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(leukotriene D4; QSAR to develop anti-**asthmatic** drugs)

IT 1657-53-0P 1694-19-5P 18493-15-7P 123871-49-8P 354803-28-4P 354803-30-8P 354803-31-9P 354803-32-0P 354803-34-2P 354803-37-5P 354803-38-6P 354803-39-7P 354803-40-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(QSAR to develop anti-**asthmatic** drugs)

IT 56-53-1, Diethylstilbestrol 103-16-2, 4-Benzyloxy-phenol 327-97-9, Chlorogenic acid 19221-08-0, 4-Hydroxy-4'-nitrostilbene 34541-73-6 133005-88-6 354803-27-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(QSAR to develop anti-**asthmatic** drugs)

IT 100-52-7D, Benzaldehyde, methoxy derivs., reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(QSAR to develop anti-**asthmatic** drugs)

L7 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB Apigenin (4',5,7-trihydroxyflavone) is an activator of **cystic fibrosis** transmembrane conductance regulator (CFTR)-mediated Cl- currents across epithelia at low concns. and a blocker at high concns. We detd. the roles of structural components of apigenin for both stimulation and block of Cl- currents across Calu-3 epithelia. The half-maximal binding affinity of apigenin for current stimulation (Ks) was 9.1 .+-. 1.3 .mu.M, and the rank-order of mol. structures was 7-hydroxyl > pyrone = 4'-hydroxyl > 5-hydroxyl. Both the 7-hydroxyl and the 4'-hydroxyl served as H-bond acceptors, whereas the 5-hydroxyl was an H-bond donor. The half-maximal binding affinity of apigenin during current block was 74 .+-. 11 .mu.M. Blocked Cl- currents were structurally detd. by 7-hydroxyl = 4'-hydroxyl > pyrone > 5-hydroxyl. Prestimulation of tissues with forskolin significantly affected activation kinetics and binding characteristics. After forskolin stimulation, Ks was 4.1 .+-. 0.9 .mu.M, which was structurally detd. by pyrone > all hydroxyls > single hydroxyls. In contrast, block of Cl- current by apigenin was not affected by forskolin stimulation. We conclude that apigenin binds to a stimulatory and an inhibitory binding site, which are distinguished by their affinities and the mol. interactions during binding.

ACCESSION NUMBER: 2000:910656 CAPLUS
DOCUMENT NUMBER: 134:187833
TITLE: Structural determinants for activation and block of

CFTR-mediated chloride currents by apigenin

AUTHOR(S): Illek, Beate; Lizarzaburu, Mike E.; Lee, Vivien; Nantz, Michael H.; Kurth, Mark J.; Fischer, Horst

CORPORATE SOURCE: Children's Hospital Oakland Research Institute, Oakland, CA, 94609, USA

SOURCE: American Journal of Physiology (2000), 279(6, Pt. 1), C1838-C1846
CODEN: AJPHAP; ISSN: 0002-9513

PUBLISHER: American Physiological Society

DOCUMENT TYPE: Journal

LANGUAGE: English

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Apigenin (4',5,7-trihydroxyflavone) is an activator of **cystic fibrosis** transmembrane conductance regulator (CFTR)-mediated Cl- currents across epithelia at low concns. and a blocker at high concns. We detd. the roles of structural components of apigenin for both stimulation and block of Cl- currents across Calu-3 epithelia. The half-maximal binding affinity of apigenin for current stimulation (Ks) was 9.1 .+-. 1.3 .mu.M, and the rank-order of mol. structures was 7-hydroxyl > pyrone = 4'-hydroxyl > 5-hydroxyl. Both the 7-hydroxyl and the 4'-hydroxyl served as H-bond acceptors, whereas the 5-hydroxyl was an H-bond donor. The half-maximal binding affinity of apigenin during current block was 74 .+-. 11 .mu.M. Blocked Cl- currents were structurally detd. by 7-hydroxyl = 4'-hydroxyl > pyrone > 5-hydroxyl. Prestimulation of tissues with forskolin significantly affected activation kinetics and binding characteristics. After forskolin stimulation, Ks was 4.1 .+-. 0.9 .mu.M, which was structurally detd. by pyrone > all hydroxyls > single hydroxyls. In contrast, block of Cl- current by apigenin was not affected by forskolin stimulation. We conclude that apigenin binds to a stimulatory and an inhibitory binding site, which are distinguished by their affinities and the mol. interactions during binding.

ST **cystic fibrosis** transmembrane conductance regulator chloride transport apigenin airway; flavonoid **resveratrol** apigenin structure activity CFTR chloride transport

IT CFTR (**cystic fibrosis** transmembrane conductance regulator)
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(structural determinants for activation and block of CFTR-mediated chloride currents by apigenin)

IT 437-64-9, Genkwanin 480-40-0, 5,7-Dihydroxy-flavone 480-44-4 **501-36-0**, trans-**Resveratrol** 520-36-5, Apigenin 525-82-6, Flavone 2196-14-7, 4',7-Dihydroxy-flavone 5631-70-9 6665-67-4, 4',5-Dihydroxy-flavone 29376-68-9, Thevetiaflavone
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(structural determinants for activation and block of CFTR-mediated chloride currents by apigenin)

L7 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS

AB Compns. and methods for therapy of **cystic fibrosis** and other conditions are provided. The compns. comprise one or more compds. such as flavones and/or isoflavones capable of stimulating chloride transport in epithelial tissues. Therapeutic methods involve the administration (e.g., orally or via inhalation) of such compns. to a patient afflicted with **cystic fibrosis** and/or another

condition responsive to stimulation of chloride transport.

ACCESSION NUMBER: 1999:265881 CAPLUS
DOCUMENT NUMBER: 130:306615
TITLE: Flavonoids for **cystic fibrosis** therapy
INVENTOR(S): Fischer, Horst Bernhard; Illek, Beate
PATENT ASSIGNEE(S): Children's Hospital Oakland Research Institute, USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9918953 | A1 | 19990422 | WO 1998-US21887 | 19981016 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 5972995 | A | 19991026 | US 1997-951912 | 19971016 |
| AU 9910939 | A1 | 19990503 | AU 1999-10939 | 19981016 |
| EP 1024803 | A1 | 20000809 | EP 1998-953609 | 19981016 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.: US 1997-951912 A 19971016
WO 1998-US21887 W 19981016
OTHER SOURCE(S): MARPAT 130:306615
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Flavonoids for **cystic fibrosis** therapy

AB Compns. and methods for therapy of **cystic fibrosis** and other conditions are provided. The compns. comprise one or more compds. such as flavones and/or isoflavones capable of stimulating chloride transport in epithelial tissues. Therapeutic methods involve the administration (e.g., orally or via inhalation) of such compns. to a patient afflicted with **cystic fibrosis** and/or another condition responsive to stimulation of chloride transport.

ST flavonoid chloride transport **cystic fibrosis** therapy

IT CFTR (**cystic fibrosis** transmembrane conductance regulator)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(508-dephenylalanine-, and 551 point mutation CFTR protein; flavonoids for **cystic fibrosis** therapy)

IT Gallbladder
Intestine
Mammary gland
Pancreas
Pancreas
Respiratory tract
Salivary gland
Salivary gland

Sweat gland
Sweat gland
(epithelium; flavonoids for **cystic fibrosis** therapy)

IT Biological transport
**Cystic fibrosis**
Epithelium
(flavonoids for **cystic fibrosis** therapy)

IT Flavones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavonoids for **cystic fibrosis** therapy)

IT CFTR (**cystic fibrosis** transmembrane conductance regulator)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(flavonoids for **cystic fibrosis** therapy)

IT Drug delivery systems
(inhalants; flavonoids for **cystic fibrosis** therapy)

IT Flavones
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(isoflavones; flavonoids for **cystic fibrosis** therapy)

IT Drug delivery systems
(oral; flavonoids for **cystic fibrosis** therapy)

IT Phenols, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyphenols, nonpolymeric; flavonoids for **cystic fibrosis** therapy)

IT 50-81-7, Ascorbic acid, biological studies 50-81-7D, Ascorbic acid, salts 56-81-5, 1,2,3-Propanetriol, biological studies 67-68-5, Dimethylsulfoxide, biological studies 74-89-5, Methylamine, biological studies 117-39-5, Quercetin 153-18-4, Rutin 156-54-7, Sodium butyrate 446-72-0, Genistein 480-44-4 486-66-8, Daidzein 487-26-3, Flavanone 487-26-3D, derivs. 490-83-5, Dehydroascorbic acid 491-80-5, Biochanin A **501-36-0**, **Resveratrol** 520-18-3 520-36-5, Apigenin 525-82-6, Flavone 525-82-6D, derivs. 528-48-3, Fisetin 552-59-0, Prunetin 574-12-9D, derivs. 1184-78-7, Trimethylamine N-oxide 1821-12-1, 4-Phenylbutyric acid 4737-27-3D, derivs. 17306-46-6, Apigenin 7-O-neohesperidoside 23522-05-6, Taurin 89149-10-0, Deoxyspergualin 223525-13-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(flavonoids for **cystic fibrosis** therapy)

IT 16887-00-6, Chloride, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(flavonoids for **cystic fibrosis** therapy)

L7 ANSWER 7 OF 8 USPATFULL

AB This invention relates to a method of treating and preventing inflammatory disorders and related conditions using an extract of

feverfew. Particularly, the invention includes a method of treating and preventing inflammatory disorders and related conditions which comprises applying a topical composition comprising an effective amount of an extract of feverfew to a patient and a method of treating and preventing inflammatory disorders and related conditions of the skin by applying a topical composition containing an effective amount of an extract of feverfew to a patient. In addition, the invention includes a method of treating and preventing inflammatory disorders and related conditions by applying a topical composition containing an effective amount of an extract of feverfew to a patient where said extract is substantially free of .alpha.-unsaturated .gamma.-lactone.

ACCESSION NUMBER: 2002:152243 USPATFULL
TITLE: Method for the topical treatment and prevention of inflammatory disorders and related conditions using extracts of feverfew (Tanacetum parthenium)
INVENTOR(S): Callaghan, Theresa, Ax Delft, NETHERLANDS
Oddos, Thierry, Meudon, FRANCE
Gendimenico, Gerard, Neshanic Station, NJ, United States
Martin, Katharine, Ringoes, NJ, United States
PATENT ASSIGNEE(S): Johnson & Johnson Consumer France SAS I3540, FRANCE (non-U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 6410062 | B1 | 20020625 |
| APPLICATION INFO.: | US 2000-586587 | | 20000602 (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 1999-137332P | 19990603 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Prats, Francisco
ASSISTANT EXAMINER: Coe, Susan D.
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 682

DETD . . . or prevented by topical use of the compositions of this invention include, but are not limited to the following: arthritis, **bronchitis**, contact dermatitis, atophic dermatitis, psoriasis, seborrheic dermatitis, eczema, allergic dermatitis, polymorphous light eruptions, inflammatory dermatoses, folliculitis, alopecia, poison ivy, insect. . .

DETD . . . antioxidants such as sulfhydryl compounds and their derivatives (for example, sodium metabisulfite and N-acetyl-cysteine, acetyl-cysteine), lipoic acid and dihydrolipoic acid, **resveratrol**, lactoferin, ascorbic acid and ascorbic acid derivatives (for example ascorbyl palmitate and ascorbyl polypeptide). Oil soluble antioxidants suitable for use. . .

L7 ANSWER 8 OF 8 USPATFULL
AB Compositions and methods for therapy of **cystic fibrosis** and other conditions are provided. The compositions comprise one or more flavones and/or isoflavones capable of stimulating chloride transport in epithelial tissues. Therapeutic methods involve

the administration (e.g., orally or via inhalation) of such compositions to a patient afflicted with **cystic fibrosis** and/or another condition responsive to stimulation of chloride transport.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

| | |
|---|---|
| ACCESSION NUMBER: | 1999:132877 USPATFULL |
| TITLE: | Compositions and methods for **cystic fibrosis** therapy |
| INVENTOR(S): | Fischer, Horst Bernhard, Albany, CA, United States<br>Illek, Beate, Albany, CA, United States |
| PATENT ASSIGNEE(S): | Children's Hospital Medical Center of Northern California, Oakland, CA, United States (U.S. corporation) |

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 5972995 | | 19991026 | |
| APPLICATION INFO.: | US 1997-951912 | | 19971016 | (8) |

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| PRIMARY EXAMINER: | Weddington, Kevin E. |
| LEGAL REPRESENTATIVE: | Seed and Berry LLP |
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| EXEMPLARY CLAIM: | 1 |
| NUMBER OF DRAWINGS: | 9 Drawing Figure(s); 9 Drawing Page(s) |
| LINE COUNT: | 1698 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Compositions and methods for **cystic fibrosis** therapy

AB Compositions and methods for therapy of **cystic fibrosis** and other conditions are provided. The compositions comprise one or more flavones and/or isoflavones capable of stimulating chloride transport in. . . epithelial tissues. Therapeutic methods involve the administration (e.g., orally or via inhalation) of such compositions to a patient afflicted with **cystic fibrosis** and/or another condition responsive to stimulation of chloride transport.

SUMM The present invention relates generally to the treatment of **cystic fibrosis**. The invention is more particularly related to compositions comprising one or more flavones and/or isoflavones, which may be used to. . . (ie., absorption and/or secretion) in epithelial tissues of the airways, the intestine, the pancreas and other exocrine glands, and for **cystic fibrosis** therapy.

SUMM **Cystic fibrosis** is a lethal genetic disease afflicting approximately 30,000 individuals in the United States. Approximately 1 in 2500 caucasians is born. . .

SUMM **Cystic fibrosis** affects the secretory epithelia of a variety of tissues, altering the transport of water, salt and other solutes into and. . . in the airways, pancreas and other tissues to transport chloride ions, and accompanying sodium and water, is severely reduced in **cystic fibrosis** patients, resulting in respiratory, pancreatic and intestinal ailments. The principle clinical manifestation of **cystic fibrosis** is the resulting respiratory disease, characterized by airway obstruction due to the presence of a thick mucus that is difficult. . .

SUMM In **cystic fibrosis**, defective chloride transport is generally due to a mutation in a chloride channel known as the **cystic fibrosis** transmembrane conductance regulator

(CFTR; see Riordan et al., Science 245:1066-73, 1989). CFTR is a linear chloride channel found in the. . . of which is a deletion of phenylalanine at position 508 (.DELTA.F508-CFTR), which is present in approximately 70% of patients with **cystic fibrosis**. A glycine to aspartate substitution at position 551 (G55 ID-CFTR) occurs in approximately 1% of **cystic fibrosis** patients.

SUMM Current treatments for **cystic fibrosis** generally focus on controlling infection through antibiotic therapy and promoting mucus clearance by use of postural drainage and chest percussion.. . .

SUMM Accordingly, improvements are needed in the treatment of **cystic fibrosis**. The present invention fulfills this need and further provides other related advantages.

SUMM Briefly stated, the present invention provides compositions and methods for the therapy of **cystic fibrosis**. Within one aspect, the present invention provides methods for enhancing chloride transport in epithelial cells, comprising contacting epithelial cells with. . .

SUMM Within other aspects, the present invention provides methods for treating **cystic fibrosis** in a patient, comprising administering a compound selected from the group consisting of flavones and isoflavones, wherein the compound is. . .

SUMM . . . aspects, the present invention provides methods for increasing chloride ion conductance in airway epithelial cells of a patient afflicted with **cystic fibrosis**, wherein the patient's CFTR protein has a deletion at position 508, the method comprising administering to a mammal one or. . .

SUMM Within further aspects, pharmaceutical compositions for treatment of **cystic fibrosis** are provided, comprising one or more flavones or isoflavones capable of stimulating chloride transport in combination with a pharmaceutically acceptable. . .

DETD . . . generally directed to compositions and methods for the treatment of diseases characterized by defective chloride transport in epithelial tissues, including **cystic fibrosis**, and diseases with excessive accumulation of mucus, including **cystic fibrosis**, chronic **bronchitis** and **asthma**. It has been found, within the context of the present invention, that certain flavones and isoflavones are capable of stimulating. . . pancreas and other exocrine glands) in a cyclic-AMP independent manner. Such therapeutic compounds may be administered to patients afflicted with **cystic fibrosis** as described herein.

DETD . . . assay for evaluating chloride transport, cells are transfected with a chloride channel gene (e.g., CFTR) having a mutation associated with **cystic fibrosis**. Any CFTR gene that is altered relative to the normal human sequence provided in SEQ ID NO: 1, such that the encoded protein contains a mutation associated with **cystic fibrosis**, may be employed within such an assay. The most common disease-causing mutation in **cystic fibrosis** is a deletion of phenylalanine at position 508 in the CFTR protein (.DELTA.F508-CFTR; SEQ ID NO:4). Accordingly, the use of. . .

DETD . . . or isoflavone that stimulates chloride transport within at least one of the above assays may be used for therapy of **cystic fibrosis**, other diseases characterized by abnormally high mucus accumulation in the airways or intestinal disorders such as constipation. Preferred therapeutic compounds. . .

DETD . . . compositions are administered in an amount, and with a frequency, that is effective to inhibit or alleviate the symptoms of **cystic fibrosis** and/or to delay the progression of the

disease. The effect of a treatment may be clinically determined by nasal potential. . .

DETD As noted above, a pharmaceutical composition may be administered to a mammal to stimulate chloride transport, and to treat **cystic fibrosis**. Patients that may benefit from administration of a therapeutic compound as described herein are those afflicted with **cystic fibrosis**. Such patients may be identified based on standard criteria that are well known in the art, including the presence of abnormally high salt concentrations in the sweat test, the presence of high nasal potentials, or the presence of a **cystic fibrosis**-associated mutation. Activation of chloride transport may also be beneficial in other diseases that show abnormally high mucus accumulation in the airways, such as **asthma** and chronic **bronchitis**. Similarly, intestinal constipation may benefit from activation of chloride transport by a flavone or isoflavone as provided herein.

CLM What is claimed is:

12. A method for treating **cystic fibrosis** in a mammal, comprising administering to a mammal one or more compounds selected from the group consisting of flavones and. . .

17. A method for increasing chloride ion conductance in airway epithelial cells of a patient afflicted with **cystic fibrosis**, wherein the patient's CFTR protein has a deletion at position 508, the method comprising administering to a mammal one or. . .

18. A pharmaceutical composition for treatment of **cystic fibrosis**, comprising one or more flavones or isoflavones capable of stimulating chloride secretion in combination with a pharmaceutically acceptable carrier, where. . .

19. A pharmaceutical composition for treatment of **cystic fibrosis**, comprising quercetin in combination with a pharmaceutically acceptable carriers and wherein the composition further comprises 4-phenylbutyrate.

20. A pharmaceutical composition for treatment of **cystic fibrosis**, comprising apigenin in combination with a pharmaceutically acceptable carrier, and wherein the composition further comprises 4-phenylbutyrate.

21. A pharmaceutical composition for treatment of **cystic fibrosis**, comprising kaempferol in combination with a pharmaceutically acceptable carriers and wherein the composition further comprises 4-phenylbutyrate.

22. A pharmaceutical composition for treatment of **cystic fibrosis**, comprising biochanin A in combination with a pharmaceutically acceptable carrier, and wherein the composition further comprises 4-phenylbutyrate.

IT 50-81-7, Ascorbic acid, biological studies 50-81-7D, Ascorbic acid, salts 56-81-5, 1,2,3-Propanetriol, biological studies 67-68-5, Dimethylsulfoxide, biological studies 74-89-5, Methylamine, biological studies 117-39-5, Quercetin 153-18-4, Rutin 156-54-7, Sodium butyrate 446-72-0, Genistein 480-44-4 486-66-8, Daidzein 487-26-3, Flavanone 487-26-3D, derivs. 490-83-5, Dehydroascorbic acid 491-80-5, Biochanin A **501-36-0**, Resveratrol 520-18-3 520-36-5, Apigenin 525-82-6, Flavone 525-82-6D, derivs. 528-48-3, Fisetin 552-59-0, Prunetin 574-12-9D, derivs. 1184-78-7,

Trimethylamine N-oxide 1821-12-1, 4-Phenylbutyric acid 4737-27-3D, derivs. 17306-46-6, Apigenin 7-O-neohesperidoside 23522-05-6, Taurin 89149-10-0, Deoxyspergualin 223525-13-1
(flavonoids for cystic fibrosis therapy)

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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      47.94     111.85

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
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     (FILE 'HOME' ENTERED AT 20:15:59 ON 11 JUL 2002)

     FILE 'REGISTRY' ENTERED AT 20:16:18 ON 11 JUL 2002
               E RESVERATROL/CN
L1             1 S E3

     FILE 'STNGUIDE' ENTERED AT 20:17:20 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:24:43 ON 11 JUL 2002
L2          1307 S (L1 OR RESVERATROL?)
L3             7 S L2 AND RESPIRAT? AND INFLAMMAT? AND (ASTHMA? OR ALVEOLITI? OR
L4             7 DUP REM L3 (0 DUPLICATES REMOVED)

     FILE 'STNGUIDE' ENTERED AT 20:36:40 ON 11 JUL 2002

     FILE 'CAPLUS, USPATFULL' ENTERED AT 20:40:02 ON 11 JUL 2002
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| L5 | 16 | S L2 AND (ASTHMA? OR ALVEOLITI? OR COPD OR CHRONIC(2A)OBSTRUCT? |
| L6 | 15 | DUP REM L5 (1 DUPLICATE REMOVED) |
| L7 | 8 | S L6 NOT L3 |